A. M. A.
ARCHIVES OF
NEUROLOGY ᴬɴᴅ PSYCHIATRY

APRIL 1953
VOLUME 69   NUMBER 4

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of the American Medical Association

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PSYCHOTIC REACTIONS IN PROBLEM DRINKERS TREATED WITH DISULFIRAM (ANTABUSE)

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A PROGRAM for the treatment of problem drinkers with disulfiram (antabuse) [1] was instituted at the clinic in April, 1949. The purpose of the study has been to investigate the psychologic, pharmacologic, and therapeutic effects of this treatment and to determine whether disulfiram is a safe drug to use in the treatment of alcoholism.

MATERIAL AND METHOD

Selection of patients for preliminary study was limited to those with a chief complaint of alcoholism. Approximately one-half the patients came of their own volition; 10 were transfers from a state hospital and under commitment for alcoholism, and the remainder were referred by spouse, physician, employer, or other person. One out of five patients asking for treatment by telephone failed to keep a first appointment. Approximately one patient out of seven who kept the appointment decided that he did not want this type of treatment after hearing that it was not a "quick and easy cure" or that he would not be able to drink at all during the treatment. Several patients failed to complete preliminary studies and expressed various rationalizations for their not doing so. Three were refused treatment because of physical disease (recent myocardial infarction, diabetes mellitus, and liver disease respectively), and three were dropped early in the course of the treatment because of abnormal findings in the electrocardiograms made at the time of alcohol trials.[2] None were refused treatment because of psychiatric problems in addition to alcoholism or because of anticipated poor prognosis. Up to the present time 120 patients have been interviewed, and disulfiram medication has been started with 96.

For the initial studies and treatment, 20 of the patients were hospitalized; the rest were managed on an outpatient basis. Pretreatment investigation included a thorough psychiatric history and personality evaluation, physical and neurologic examinations, laboratory studies, and, for most, a Minnesota Multiphasic Personality Inventory. If no physical contraindication was found, medication with disulfiram was instituted, and trial drinks were given at the hospital on the 5th and 12th days. During the disulfiram-alcohol reaction, extensive pharmacologic

testing was done on 51 of the patients[a]; electrocardiographic recordings were made on most, and clinical responses were carefully observed in all. A maintenance dose of disulfiram was determined on the basis of the severity of clinical reaction to the trial drinks. About equal numbers of the patients required daily doses of 0.25 and 0.5 gm., and only a few required 0.75 or 1.0 gm.

Of the 96 patients for whom treatment was instituted, all but 2 were considered to be of the middle social class. Nine were or had been in professional occupations, and occupational spread below this level revealed a fair sampling of an urban population. The ages ranged from 25 to 67, with a median age of 42. There were 75 men and 21 women. The duration of problem drinking, as estimated by the examiner, varied from 2 to 26 years, with an average of 13.7 years. The initial diagnoses in the group included essential alcoholism, 80 patients; alcoholism secondary to psychoneurosis, 12 patients; alcoholism secondary to schizophrenia, 2 patients; alcoholism secondary to manic-depressive psychosis, 1 patient, and chronic alcoholism with mental deterioration, 1 patient. It is of some interest that the two patients with the diagnosis of alcoholism secondary to schizophrenia were both among a very small group who came to the clinic to talk frankly of their desire to discontinue disulfiram treatment before doing so.

PSYCHOTIC REACTIONS

During the course of treatment and follow-up study of the patients beginning disulfiram medication, 13 (13.5%) were known to have had psychotic reactions. Three of these patients are not reported on in detail here because the onset of the psychotic reaction occurred $2\frac{1}{2}$, 12, and 14 months after the discontinuation of treatment. Certain details of the 10 cases of psychosis occurring during the course of treatment with disulfiram are summarized in the Table, and the individual cases are reported.

Six patients with an initial diagnosis of essential alcoholism incurred psychotic reactions: four, a depression; one, a catatonic schizophrenia reaction, and one, Korsakoff's psychosis. Of two patients with an initial diagnosis of alcoholism secondary to psychoneurosis, one had a psychotic depression, and one, a paranoid schizophrenia reaction. The patient whose initial diagnosis was alcoholism secondary to manic-depressive psychosis had a manic reaction, and the patient with mental deterioration due to alcohol displayed a paranoid psychosis.

Only one of these patients (Case 10) exhibited a reaction that was clearly of an organic type. It could not categorically be determined whether the Korsakoff psychosis was due primarily to a toxic effect of the drug administered. However, this patient later returned to the prolonged use (two months) of the same dose of disulfiram without a recurrence of the psychotic reaction. Two others displayed clinical pictures that had features suggestive, but not definitely diagnostic, of an organic reaction. The first patient (Case 6) had impaired memory for the events of the preceding two days, a panic reaction with rapid changes in the intensity of fear, and very active production of fearful fantasies and dream material. However, all the productions could be understood as paranoid projections, and at no time were there illusions or hallucinatory experiences. The other patient (Case 9) had transient confusion and slurred speech three weeks prior to the onset of a manic excitement.

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3. Hine, C. H.; Anderson, H. H.; Macklin, E. A.; Burbridge, T. N.; Simon, A., and Bowman, K. M.: Some Observations on the Effects of Small Doses of Alcohol in Patients Receiving Tetraethylthiuramdisulphide (Antabuse), J. Pharmacol. & Exper. Therap. **98**:13, 1950. Hine, C. H.; Burbridge, T. N.; Macklin, E. A.; Anderson, H. H., and Simon, A.: Some Aspects of the Human Pharmacology of Tetraethylthiuramdisulphide (Antabuse)-Alcohol Reactions, J. Clin. Invest. **31**:317, 1952.

Data on Ten Patients in Whom Psychoses Developed During Disulfiram Therapy

No.	Sex	Age, Yr.	Problem Drinker, Yr.	Initial Diagnosis	Treatment Prior to Psychosis					Details of Psychosis				Period Disulfiram Resumed
					Disulfiram Taken, Mo.	Period of Sobriety, Mo.	Regularity on Disulfiram*	Daily Dose, Gm.	Early Side-Effects	Type	Total Duration	Treatment	Result	
1	M	43	26	Alc.	3½	5	+++	0.25	Mild	Depres.	4 wk.	Hosp.; 3 E.S.T.	Recovery	1 mo.
2	M	33	11	Alc.	2½	3	+++++	0.5	Mod.	Depres.	10 days	Hosp.	Suicide	......
3	M	40	20	Alc.	½	1	+++++	1.0	Mod.	Depres.	3 days	Hosp.	Recovery	No
4	M	37	2	Secondary to neurosis	½	0	++	0.75	Mild	Depres.	2½ mo.	Hosp.	Recovery	No
5	M	47	14	Alc.	6	6	+++	0.5	Mild	Depres.	2 mo.	Hosp.; 6 E.S.T.	Recovery	30 mo.
6	M	39	16	Secondary to neurosis	1	1½	+++	1.0	Mod.	Schiz., paranoid	10 days	Hosp.	Recovery	2 mo.
7	M	50	20	Alc.	½	4	+++	0.5	None	Schiz., catatonic	3 wk.	Hosp.; 5 E.S.T.	Recovery and Relapse	No
8	M	51	26	Chr. alc. with mental deterioration	4	1	++	0.5	Mild	Paranoia	2 wk.	Hosp.	Recovery	3 mo.
9	F	42	12	Secondary to man.-depr.	2½	½	++++	0.25	Mod.	Mania	1 wk.	Hosp.	Recovery	18 mo.
10	M	48	10	Alc.	1½	1½	++++	0.5	Mod.	Korsakoff	8 wk.	Hosp.; 5 E.S.T.	Recovery	2 mo.

* Regularity on disulfiram treatment is designated as follows: +++++ means that patient takes tablets daily by himself; ++++, that he takes tablets daily but must be reminded; +++, that he takes tablets daily but must be reminded energetically; ++, that he takes tablets irregularly.

The principal symptoms noted in the depressed patients were feelings of worthlessness, self-depreciation, hopelessness for the future, and suicidal threats and attempts. In none was there significant evidence of impaired intellectual functioning, expression of emotion other than gloom, or illusory or hallucinatory experiences. Rather characteristic of these depressions were the acuteness of onset and the rapidity of abatement of symptoms with appropriate treatment. In only one (Case 5) was the onset of the depression of an insidious character, as evidenced only by impaired professional work for six weeks prior to an impulsive suicidal attempt. This patient made a prompt recovery with six electric shock treatments in the hospital. Patient 1 was getting along well on the first job he had had in two years when he became depressed, discontinued disulfiram therapy and tried to drink cautiously. Two weeks later he telephoned the clinic to say he was going to commit suicide and to ask the therapist to explain to his wife why he had done so. He was encouraged to enter the hospital, where he showed no improvement at the end of one week, but with three electric shock treatments during the second week of hospitalization he made a complete recovery. Patient 2 was admitted to the hospital on the seventh day of his depression, demanded his release, against medical advice, two days later, and on the next day took his own life. Patient 3 had a fearful anticipation of a severe reaction to the trial drinks. Six days after a very mild reaction to his first alcohol trial he felt that the treatment was going to fail and started to drink. He experienced only severe hang-over symptoms in the hospital, where he was admitted for two days to sober up. On leaving the hospital, he went home, took 11 tablets (5.5 gm.) of disulfiram, and started to drink a bottle of port wine. After his second 8-oz. (250-cc.) glass, he said, "I know I am going to die, so may as well die happy," and drank a third glassful. He was admitted to the hospital soon after with a severe disulfiram-alcohol reaction. The total action was felt to be a suicide attempt. He made a spontaneous recovery, but disulfiram treatment was not again begun. Patient 4 had continued to drink small amounts of alcohol throughout a two-week period of disulfiram treatment, until he finally made a serious, and almost successful, suicidal attempt by slashing his wrists and throat. He would not voluntarily enter the hospital, and it was necessary to have him committed by his family to a state mental hospital, where he made an uneventful recovery in the course of 2½ months.

The patient who had a paranoid psychosis (Case 8) was admitted to the hospital on the eighth day of the psychotic reaction. His predominant symptoms were depression and fear of retaliation from persons whom he might have hurt in years past. His memory was good, and there was neither confusion nor apparent increase in intellectual dysfunction over the mental deterioration previously noted. In the hospital his fears rapidly abated, until at the end of one week no expression of paranoid ideas could be elicited. Patient 7 had onset of his catatonic schizophrenia reaction after only seven days of disulfiram medication (4.5 gm.). One week prior to commencing disulfiram treatment, this patient had had a cerebral blood flow test and had been considerably upset by the procedure. He was sure he was to have another such test at the time of his first alcohol trial. It is believed that fear of the procedure may have been a factor in the precipitation of the psychotic break. Disulfiram therapy was continued for two days but was then discontinued, as the patient had regressed to the point of confusion, hyperactivity, disorganized thinking, expression of ideas of reference, and inappropriate behavior. Three days later he

was combative and negativistic and required tube feeding. In the second week of this reaction electric shock treatment was begun, and he appeared to have recovered after five such treatments. However, a few days later he began to relapse slowly to the previous catatonic excitement, from which he recovered spontaneously only after four months.

The condition of Patient 6 who, as noted above, had symptoms suggestive of a toxic psychosis, was nevertheless thought to be more typical of paranoid schizophrenia (homosexual panic). He had a complete remission within six days, and later treatment with disulfiram was again started; he took the drug regularly for two months while in the hospital, without a relapse. Patient 9, with a prodrome of slurred speech, was admitted to the hospital on the second day of a full-blown manic excitement and made a spontaneous recovery in two weeks.

Disulfiram was withheld from all these patients when they were admitted to the hospital for the psychosis (after the second day of the reaction in the case of the patient who was hospitalized at the time of onset). This was done because it was not known to what extent the drug might be acting as a toxic agent, or whether it had a special psychologic meaning to the patient. It was thought that if the drug had either significance, recovery would be enhanced by its removal. Disulfiram therapy was reinstituted after recovery from the psychotic reactions in six of the patients. It was continued thereafter for periods ranging from 1 to 30 months without a single recurrence of a psychotic episode, except in Case 9, in which a bromide intoxication developed at a later date.

The period of disulfiram medication prior to the onset of psychosis varied from 1 week to 6 months, with an average of 9.5 weeks. The total dose of disulfiram taken during this time varied from 4.5 to 90 gm. and averaged 34 gm. The daily maintenance dose varied from 0.25 to 1.0 gm. The higher-than-average daily dose (above 0.5 gm.) taken by three patients in this reported group occurred in two cases in the early period of treatment, during which alcohol trials had not been completed. In the third case, a 1.0-gm. dose was required to produce more than the mildest reaction to one drink of whisky. The occurrence and severity of early "toxic" side-effects in this reported group were of no greater incidence than in the total group treated at this clinic.

Only 2 of the 10 patients had taken disulfiram regularly of their own volition prior to the psychosis; 4 others had taken it regularly, but only on the insistence of another person, and 2 had been irregular in its use. Three of the patients had not maintained sobriety during the treatment period prior to the development of a psychosis. The duration of sobriety for the others varied from six weeks to six months. There is no apparent relation of the onset of the psychosis to the size of the daily dose of disulfiram, the duration of treatment, or the duration of sobriety. There is a positive relation of poor cooperation on the part of the patients with the prescribed treatment program prior to the psychosis to the occurrence of psychosis, as compared with the rest of the treated group. This correlation is noted particularly in regard to outside pressure exerted to continue the medication, drinking while taking disulfiram, and expressions of doubt of the effectiveness of the treatment. However, it is difficult to evaluate the "psychosis-prevention value" of early discontinuation of disulfiram in the remainder of the treated group. Half the patients starting the medication did not complete six months of treatment. Yet the psychotic

patients, with only one exception (Case 4), willingly continued with the clinic for treatment of the psychosis and thereafter. (This may be a comment only on the greater dependence on the clinic, albeit probably hostile, of the patients who reacted with psychoses.) Lack of cooperation with the treatment program in the total treated group, as evidenced by irregularity and early discontinuation of treatment, was found to have a significant positive correlation with more severly neurotic and psychotic profiles on the Minnesota Multiphasic Personality Inventory.

CASES REPORTED IN LITERATURE

In the literature [4] 47 cases were reported in which a psychotic or a severe neurotic reaction developed while the patient was taking disulfiram. Among several authors who reported the number of psychotic reactions in the total group treated, there is agreement within the probabilities of chance as to the incidence of psychotic reactions which occur when problem drinkers are treated with disulfiram. Bennett and associates [4d] reported psychotic reactions in 6 of 37 patients treated; Usdin,[4e,j] in 3 of 38 patients treated; Bowman and associates,[4g] in 10 of 82 patients treated; Gottesfeld and associates,[4h] in 8 of 42 patients treated, and Wolff,[4l] in 5 of 22 patients treated. Martensen-Larsen [4i] reported 9 cases among more than 1,300 in which he felt the psychosis was clearly of toxic origin, but no statement is made as to whether his report included all the psychotic reactions observed. It would be interesting to make comparisons and draw conclusions from all the studies together; however, this is impossible because of the authors' failure to indicate such matters as the period of problem drinking and initial diagnosis in some of the reports, and particularly the lack of information relative to the period of disulfiram treatment, the dose taken, or the adherence of the patient to the treatment schedule prior to onset of the psychotic episode.

The types of psychotic reactions reported have been principally delirious, such as schizophrenia-like psychoses, manic excitements, and suicides. In only 14 of the cases reported, including 4 which were reported only as instances of suicide,[4l] were significant evidences of depression noted. In 5 of the 10 cases reported here, 9 of which were briefly referred to in another article,[4g] the symptomatology was clearly

4. (a) Lemieux, L. H.: L'alcoolisme chronique et ses traitements, Laval méd. **14**:1304, 1949. (b) Knutsen, B.: Complications Following Use of Antabuse in Therapy of Alcoholism, Tidsskr. norske lægefor. **69**:436, 1949. (c) Bennett, A. E.; McKeever, L. G., and Turk, R. E.: Antabuse in the Treatment of Alcoholism in a Private General Hospital, California Med. **73**:141, 1950; (d) Psychotic Reactions During Tetraethylthiuramdisulfide (Antabuse®) Therapy, J. A. M. A. **145**:483, 1951. (e) Usdin, G. L.: Antabuse in the Therapy of Chronic Alcoholism, Cincinnati J. Med. **32**:288, 1951. (f) Ostenfeld, I.: Exogenous Mania Following Antabuse Medication, Nord. med. **46**:1036, 1951. (g) Bowman, K. M.; Simon, A.; Hine, C. H.; Macklin, E. A.; Crook, G. H.; Burbridge, N., and Hanson, K.: A Clinical Evaluation of Tetraethylthiuram-disulphide (Antabuse) in the Treatment of Problem Drinkers, Am. J. Psychiat. **107**:832, 1951. (h) Gottesfeld, B. H.; Lasser, L. M.; Conway, E. J., and Mann, N. M.: Psychiatric Implications of the Treatment of Alcoholism with Tetraethylthiuram Disulfide: A Preliminary Report, Quart. J. Stud. Alcohol **12**:184, 1951. (i) Martensen-Larsen, O.: Psychotic Phenomena Provided by Tetraethylthiuram Disulfide, Quart. J. Stud. Alcohol **12**:206, 1951. (j) Usdin, G. L., and Robinson, K. E.: Psychosis Occurring During Antabuse® Administration, A. M. A. Arch. Neurol. & Psychiat. **66**:38, 1951. (k) Shaw, I. A.: Treatment of Alcoholism with Tetraethyl-thiuramdisulfide in a State Mental Hospital: A Clinical Study Based on 43 Cases, Quart. J. Stud. Alcohol **12**:576, 1951. (l) Wolff, K.: Nachteilige Nebenwirkungen bei Behandlung mit

of a "functional" depressive type. Of the six cases of psychotic reactions "of an organic type" observed by Bennett and associates,[4d] evidence of liver damage was present in five and of organic brain damage prior to treatment in four. Perhaps the differences in types of reactions observed could be explained if the specific bases for selection of patients for disulfiram treatment by the several authors were described.

Of the significant findings in the literature, two points should be noted. First, that there is general agreement on the short duration of the psychotic reactions which occur; second, there is a lack of agreement as to the etiology of these reactions.

COMMENT

It is our opinion that the psychogenic element in the psychoses which do occur has been insufficiently stressed in the literature. Dale and Ebaugh[5] have written significantly on the importance of personality structure in the disulfiram therapy of alcoholism. Although it is occasionally observed, it is not common to see psychoses develop in problem drinkers who suddenly decide to abstain, or who have been committed to a mental hospital and placed in a setting of forced sobriety. Disulfiram may have toxic effects upon cerebral function in some persons; perhaps some persons are more vulnerable than others, and the toxic action of the drug may disrupt an already precariously balanced cerebral function and lead to transitory disorganization of the personality. The rapid recovery from the various types of reactions cited may be viewed as evidence in favor of a toxic origin of the psychoses, in view of the usually rapid excretion of disulfiram. However, Shaw[4k] reported a paranoid reaction from which the patient recovered while continuing to receive the same dose of disulfiram, and three cases [4a,e] were recorded with recovery during a period in which treatment was continued in decreased doses. There is also the observation that in 10 cases, in addition to the 6 reported here, disulfiram medication was continued after recovery, though at a reduced dose in some cases, for varying periods of time, in only 1 of which was there recurrence of a psychotic episode, which was presumed to be toxic (disulfiram) in origin.[4d] Further, it is indicated that two of the patients reported here who continued medication over prolonged periods have actually gained further insight from the psychotic experiences which occurred during the treatment. Martensen-Larsen's observation that psychotic reactions are more likely to occur in patients with the severer side-effects during the period of disulfiram medication [4l] cannot be substantiated by the data in the present series. That the toxic origin of the reactions has been stressed may be due to the selection of patients treated, to the authors' failure to report "functional disorders," or to factors which cannot be determined because of lack of information.

The delusional content and the disturbed behavior patterns as manifestations of a psychotic reaction are dependent, to a large degree, on the underlying personality structure of each patient, whether considered to be induced by a drug or not. More intensive psychologic study to determine in what manner the alcoholism acts as a

dem Alkohol-Vergällungsmittel Antabus (vorläufige Mitteilung), Schweiz. med. Wchnschr. **80**:1151, 1950. (*m*) Jacobsen, E.: Deaths of Alcoholic Patients Treated with Disulfiram (Tetraethylthiuram Disulphide) in Denmark, Quart. J. Stud. Alcohol **13**:16, 1952.

5. Dale, P. W., and Ebaugh, F. G.: Personality Structure in Relation to Tetraethylthiuram-disulfide (Antabuse®) Therapy of Alcoholism, J. A. M. A. **146**:314, 1951.

defense for the individual patient, prior to the administration of disulfiram, may aid in making reasonable predictions as to patients who will be more likely to have psychotic reactions.

The hypothesis that the primary factor in the production of these psychoses is psychogenic rather than toxic fits the facts better, so far as they have been reported. It is generally accepted that for some persons the alcoholism acts as a "psychologic crutch" and that if this is removed without offering the patient some other means of support it may lead to a breakdown of the adjustment system in a dependent, regressive direction—the psychotic episode. This reaction generally leads to gratification of the dependent needs by hospitalization, special treatments, and perhaps removal of the drug. Such gratification may enable the patient to recover quickly from the psychosis.

Appropriate treatment of the psychotic reactions remains a matter to be determined by the indications in each case. If, however, the toxic origin of the psychoses is overly stressed, removal of the drug may be considered as the principal therapy. When, on the other hand, the importance of psychogenic factors is recognized, other treatment, such as hospitalization, psychotherapy, electric-shock therapy, or insulin treatment, as indicated, may speed recovery. Furthermore, and of great importance to the patient and his family, more will be enabled to have the continued benefit of disulfiram treatment.

REPORT OF CASES

CASE 1.—A man aged 43, white, married, a tool maker, was the father of two children. He had been close to his mother. His father was strict and distant. The patient was the youngest of five children. He got along well with his siblings and other children. His early development was essentially normal, with the usual childhood diseases. The most serious illnesses were pneumonia and malaria. After graduation from high school he joined the Marines, and while in the Orient he started to drink. He was married at the age of 21. He felt that, aside from trouble over his drinking, he has gotten along well with his wife. He was first committed to a state hospital for alcoholism in 1938. He then had a seven-week contact with Alcoholics Anonymous, during which he stayed sober. In April, 1947, he suffered a crippling industrial accident, eventually receiving a $10,000 settlement, and proceeded to "drink it up." In September, 1949, he was again committed to a state hospital, and one month later was transferred to this hospital for disulfiram treatment. Preliminary tests with the Minnesota Multiphasic Personality Inventory indicated a "psychopathic personality" with moderate to marked depression (D=84). It was estimated that he had been a problem drinker for 26 years. The initial diagnosis was essential alcoholism.

He was regular in treatment for 3½ months but on several occasions did try a drink. "Toxic" side-effects included mild occipital headache and dizziness. He then failed to keep clinic appointments for three weeks, drank more, and took disulfiram intermittently. He was then heard from by telephone, when he stated that he was going to commit suicide and asked the therapist to explain the hopeless nature of his illness to his wife after his death. He was encouraged to enter the hospital. The history indicated depressive symptoms of two weeks' duration. Examination disclosed a neat, clean, cooperative man, who talked freely but who had a hopeless attitude and much self-accusation. Intellectual function was considered superior. There was much evidence of masked hostility to his wife. No improvement was noted during one week in the hospital, and it was felt that the suicidal danger was great. He was then given three electric shock treatments in one week, with complete remission of depressive symptoms. On his discharge from the hospital he was instructed to resume disulfiram medication, but did so for only one month and then failed to return for visits. He has been heard from since at two- to three-month intervals, at which times he is always intoxicated and requests help for some friend who has an alcohol problem.

CASE 2.—A white man aged 33, married, a traveling salesman, recalled his mother as an ineffectual person, who was ill most of his childhood and who died in a mental hospital when he was 11 years of age. The father used alcohol moderately but was close and loving to the patient and indulged most of his whims. The patient was the older of two children, got along well with his sister, and generally was a sociable person, although he could not strike up conversation with a stranger. Drinking, which started while he was in high school, became more frequent, causing divorce from his first wife after six years of marriage. After the divorce he discontinued all social life for several months and drank very heavily. He remarried, at 28, to a very motherly woman, who gave up her own pleasures in order to be of more help to the patient. At one period he consulted a psychiatrist in regard to his drinking and kept up intermittent contact with Alcoholics Anonymous, but at no period in the 11 years of problem drinking was he able to stay sober longer than two weeks. He came to the clinic of his own volition, after hearing from a friend of the alcoholism treatment program. The initial diagnosis was essential alcoholism. He was regular in taking disulfiram and remained sober for $2\frac{1}{2}$ months, during which time he had increasing occupational success. "Toxic" side-effects included moderately severe fatigue, drowsiness, and decreased sexual potency, with mild headache in the first month of treatment. He then suddenly became depressed, had a persistent headache, and lost his appetite and interest in work. Physical and neurologic examinations revealed nothing abnormal. Two days later he telephoned from out of town to state that he felt much better, and he sounded cheerful. His wife telephoned two days later to say he was again more depressed, and she was encouraged to bring him to the clinic. When seen, he appeared very depressed, had self-accusatory ideas, felt that the future was hopeless, and admitted suicidal preoccupations; his thinking was rather disorganized. He remained in the hospital for three days, during which time his overt depressive expression decreased markedly and he formulated work plans for the immediate future. At the insistence of the patient and his wife, he was discharged from the hospital, against medical advice. The following morning he made a suicide attempt by forcing an ice pick into the side of his head above the ear. He died 12 days later in a hospital, without having regained consciousness.

CASE 3.—A male nurse aged 40, white, divorced, was the third of six children. He stated that his mother showed much affection but that the children "had to toe the mark," though he felt the younger children were allowed to do as they wished. The father was distant and drank in later years. The patient felt he was closest to and "pals with" his paternal grandmother. Irregular drinking bouts started at the age of 13 and became frequent shortly after his marriage, at the age of 20. He was divorced at 32 because of his drinking. Previous treatment included several state hospital commitments and conditioned reflex therapy. Psychiatric examination showed evidence of "psychopathic trends," and the Minnesota Multiphasic Personality Inventory showed significant elevation on the psychopathic-deviate and schizophrenic scales. Information as to numerous suicide threats to friends was not elicited until after his psychotic break. There was a very mild reaction to the first alcohol trial on the fifth day of disulfiram medication. At this time he said he had felt restless and had experienced greatly decreased sexual potency. Six days later, feeling that this treatment was going to fail, he started drinking but became very ill only on the following day. He was admitted to the hospital, where he complained of severe headache and abdominal cramps. He stated that all previous hang-overs were "babies" as compared with this one. He insisted on leaving the hospital the following day and was discharged to continue medication. One hour 10 minutes later he was readmitted to the hospital in a state approaching shock, with severe generalized erythroderma, scleral injection, tachycardia, and ataxia. His memory was slightly impaired, and there were some confusion and many complaints regarding his physical symptoms. His attention could be held for only a few moments. Cooperation and mood were variable for four days. Upon recovering, he stated that he had not taken more disulfiram, a statement which was doubted, but had bought a bottle of port wine on his way home and started to drink. With the second 8-oz. glass he noted onset of heat, palpitation, and shortness of breath. He stated that by the time he finished the glass he felt he was "surely going to die, so I might as well die happy," and drank a third glass. Disulfiram treatment was discontinued after this episode, which seemed so clearly a suicidal attempt. Two months later he made a suicidal attempt with bromides.

CASE 4.—A white man aged 37, a skilled laborer, separated from his wife, was an only child. His father was a locomotive engineer and was frequently away from home, but was kind and affectionate. His mother was "not understanding, or openly affectionate, and angered easily." Social drinking started shortly after the patient was married, at the age of 25. Five years later, when the patient's father died and his mother took a more active part in his family, drinking became a two- to three-day weekend habit. Two years prior to admission to the clinic his wife separated from him, and the patient had since lived with his mother. For the past year he had consumed at least 1 pint (500 cc.) of whisky a day. He was brought to the clinic by his mother. Clinical evaluation indicated a mixed psychoneurosis, and the Minnesota Multiphasic Personality Inventory showed a psychopathic personality (or character neurosis) with moderate depression and paranoid trends. He took disulfiram irregularly, for only two weeks, and during this period tried to drink on several occasions. During this period he complained of mild fatigue and diarrhea. On one of these occasions he had a convulsion, apparently induced by a disulfiram-alcohol reaction. Except for this marked lack of cooperation, his depression was not recognized until he made a serious suicidal attempt by slashing his wrists and throat. His depression continued after recovery from the acute surgical condition, and, as he was not cooperative, he was committed to a state mental hospital, where he made an uneventful recovery in 2½ months. Word has been received that he has returned to excessive drinking since his discharge.

CASE 5.—A white man aged 47, married, an attorney, was the oldest of three children. There was always a close emotional tie with his mother. She was ambitious for him, and he strove to please her with good grades. On occasion he would deliberately eat green apples in order to become sick enough to gain her attention. His father was distant toward him. His marriage, since the age of 29, had been complicated by his wife's chronic paranoid illness. Excessive drinking had gradually increased over a 14-year period. Bouts occurred at approximately six-month intervals and lasted from one to four weeks. His professional work had failed to such a degree that his partners threatened to dissolve the business. Previous treatment included two conditioned reflex treatments and meetings with Alcoholics Anonymous, which he dropped because the other members were "socially inferior." During the first month of disulfiram treatment he complained of mild nausea, loss of appetite, and confusion. He took the drug regularly and remained sober for four months. Then depression set in insidiously, and he became irregular in medication. Two months later he took an overdose of barbiturate, with suicidal intent. He was then admitted to the hospital, where he made a rapid recovery with six electric-shock treatments. On discharge from the hospital, he again began disulfiram therapy and has taken the drug regularly for 30 months, without complication.

CASE 6.—A white man aged 39, a cannery inspector, separated from his wife, was the sixth of eight children. Two brothers were alcoholic, and one sister had had a "nervous breakdown." He had a poor relationship with his father, whom he described as strict, punitive, domineering, and dissatisfied. His mother was undemonstrative, depressed at times, and unhappy with her husband. She was permissive with the children. The patient had been a bed wetter until the age of 15 and had numerous anxiety attacks during childhood. He had the usual childhood diseases and acquired gonorrhea and syphilis at the age of 18. He made one common-law marriage to a woman 10 years older than himself and had a child by her. He then left her, married another older woman, divorced her, and had legally married his first wife. He was drinking regularly at the age of 22, as he felt it helped him meet people in his work as a salesman. He had lost many jobs because of drinking. Previous, unsuccessful treatment included psychotherapy and a medical approach. Clinical evaluation at the time of admission was that of drinking secondary to a severe psychoneurotic problem. The Minnesota Multiphasic Personality Inventory evidenced a psychopathic personality with a schizophrenic process and marked depression, and revealed that he was a rather submissive, dependent person—an oral character. He was hospitalized during the first month of treatment but had pass privileges. He took disulfiram regularly and remained sober. During this time he complained of moderate drowsiness and indigestion. On his discharge from the hospital there was no evidence of disturbance. However, the following day he had an acute onset of "confusion" and paranoid ideas. On the second day he appeared in a city emergency hospital "very confused," and from there he was admitted to the hospital. On admission he had poor memory for events of the preceding two days. The content of his delusional ideas was typical of acute homosexual panic. One week after onset he had recovered

his previous trend of thought and denied all delusional ideas. On his discharge from the hospital, disulfiram medication was started once more, but he failed to take the drug regularly and started drinking again. He has since been readmitted to the hospital, where he has been treated with psychotherapy and disulfiram (0.5 gm. per day) for two months, without psychotic symptoms.

CASE 7.—A white man aged 50, a gate watchman, separated from his wife, had been an almost constant state-hospital resident for 1½ years. He was the youngest of three children. His father was strict but was away from home most of the time. His mother was stern and strong-minded; she separated from his father when the patient was 8 years old. The patient felt he was never close to either parent. He had been married and divorced three times. His job status showed gradual deterioration over the years, with demotion from bay pilot to gate watchman. He had been a heavy drinker for 20 years, with no control for five years. Numerous hospitalizations had failed to achieve more than short periods of sobriety. On transfer to this hospital from the state hospital, the patient was somewhat depressed and avoided activity with the other patients. He was very disturbed by, and seemed more withdrawn after, a cerebral blood flow test, performed before administration of disulfiram. Between Nov. 29 and Dec. 6, 1949, he received 4.0 gm. of disulfiram, and had a second cerebral blood flow test with the first alcohol trial, on the latter date. The following day he was confused and hyperactive and displayed disorganized thinking, with ideas of reference and inappropriate behavior in the ward. Five days later he was negativistic and combative, though his last dose of disulfiram had been taken on Dec. 7. He made a transient recovery with five electric shock treatments in the next two weeks, but then slowly relapsed into catatonia for another four months.

CASE 8.—A white man aged 51, married, a retired special policeman, was the oldest of four children. The father, whom he described as passive and stable, died when the patient was 10 years of age. His mother, with whom he had never been happy, died when he was 12, after a mental illness of two years' duration. For 26 years he had been a problem drinker. Thirteen years prior to admission he was forced to give up drafting because of a tremor and had not worked for six years because of increasing disability. He had been married for 23 years to a woman 12 years his senior. The initial diagnosis was chronic alcoholism with mental deterioration. Between September and December, 1949, he took disulfiram irregularly and drank on several occasions, apparently not remembering his moderately severe reactions to alcohol trials. On one occasion he rendered himself unconscious. The only side-effects of which he complained were mild fatigue, headache, and nausea. For the next month his wife gave him disulfiram regularly, and he abstained from alcohol. Then, suddenly, on Jan. 4, 1950, he became withdrawn and depressed and expressed suicidal ideas and intense fear of certain people with whom he had had to deal as a policeman. He believed his life was endangered. He was admitted to the hospital one week after the onset of symptoms. Disulfiram medication was discontinued, and his problems were discussed with him in short interviews. One week later he was completely recovered from the psychotic episode. He continued to take disulfiram under his wife's direction for the next three months, without dramatic incident. Home care became more difficult, however, as the patient failed to take care of "everyday needs," and arrangements were made for custodial care.

CASE 9.—A housewife aged 42, white, had lost her father when she was a small child. The mother began to work and left the patient in care of nurses throughout childhood and adolescence. The patient characterized the nurses as strict. While in college, the patient felt that she was inferior and a misfit "because mother worked." She had been married for 16 years, was very dependent on her husband, and had a generally poor relationship with him. For 12 years she had drunk to excess. There had been approximately 40 hospitalizations for acute alcoholism in the past 10 years. She had received conditioned reflex treatment in 1944 and attended meetings of Alcoholics Anonymous sporadically between 1947 and 1949. On June 10, 1949, she started taking disulfiram; she had moderately severe vomiting and appeared "speeded up" on several occasions. On Oct. 17, 1949, confusion and slurred speech were noted. On Nov. 7, 1949, when she was seen at the clinic, her husband complained that she had become much worse. She was more confused and had marked pressure of speech and a flight of ideas. There were no delusions or hallucinations, and affect was appropriate. She was hospitalized, and disulfiram medication was discontinued. Four days later she had completely recovered and commenced disulfiram

therapy again. Two months later she was readmitted to the hospital with a severe bromide intoxication. For the next 16 months she continued irregularly to take disulfiram at a reduced dose (0.25 gm. a day), during which period she had three alcoholic bouts.

CASE 10.—A white man aged 48, a part-time salesman, married, stated that his father had been generally permissive, loving, and companionable with his children. The father had been a successful lawyer and a strict prohibitionist; he died when the patient was 14. The patient was close to and loved and admired his self-sacrificing mother, who was sick much of his childhood. She was ambitious for him but not demanding. He had an older sister and a younger brother, upon whom he had leaned heavily in recent years. He had been married 22 years to a woman who has been self-sacrificing and not punitive regarding his drinking. As an adolescent and young man his health was good and he was socially active. He progressed from mechanic to owner of an automobile agency in 15 years. With this success drinking began. This increased to an excess in six years, and two years later his business failed. He had found only intermittent work as a used-car salesman in the eight years since. The initial examination was not remarkable except that he appeared 10 years older than his stated age. The diagnosis was essential alcoholism. Disulfiram medication was started on March 10, 1950. The early side-effects were moderately severe, with drowsiness, headache, abdominal cramps, and vomiting; and there were mild malaise and dizziness. His wife and brother thought that he was confused at times, but this was not apparent in his visits to the clinic, except that he brought in several scribbled notes regarding plans which were not always entirely intelligible to himself. He took 0.5 gm. of disulfiram daily and abstained from drinking for over six weeks. While shaving on the morning of April 27, he fell to the floor and had a mild convulsion. He was admitted to the hospital two hours later, at which time he was confused, had no memory for the immediate past, expressed vague paranoid ideas, and had hallucinations of his brother's presence. During the following days he saw many fearful, grotesque images. Within five days there were progression to confabulation, distorted elaboration of incidents observed in the ward, and disorientation for time. Rorschach findings at this time were interpreted as characteristic of Korsakoff's psychosis. He improved markedly during the next four days, and disulfiram therapy was reinstituted. Suddenly he became confused again, expressed paranoid ideas, and displayed pressure of speech and activity. During the next two weeks he received five electric shock treatments and recovered. He then did not want to resume disulfiram, but did so after a drinking bout five weeks later. He took the same dose as before for two months without incident, and then stopped at the time of a "stomach upset."

SUMMARY

1. Ten cases in which psychotic reactions developed during the course of disulfiram treatment are reported in detail.

2. The literature on such cases previously reported is discussed, with particular emphasis on the divergence of opinions concerning the principal etiologic factor.

3. The hypothesis is offered that the primary factor is psychogenic.

4. The importance of such distinction as it affects the treatment of patients who incur psychotic reactions is commented on.

VISUAL DISTURBANCES AS THE RESULT OF NYSTAGMUS ON DIRECT FORWARD GAZE

Effect of Amobarbital (Amytal®) Sodium

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BLURRING of vision is a common complaint of patients with multiple sclerosis and is usually attributed to the pallor of the optic disks, or "bitemporal pallor," frequently observed in this condition. In studying patients with acquired nystagmus on direct forward gaze (fixation nystagmus), we found that they all complained of blurred vision. A more detailed description of this symptom disclosed that the visual disturbance was actually oscillopsia, a visual sensation in which objects appear to be moving rapidly from side to side or up and down (oscillating).

It has been observed[1] that intravenous injections of barbiturates temporarily abolish fixation nystagmus and the associated sensation of oscillopsia. The present investigation consists of the intravenous administration of barbiturates to patients with and without evidence of pallor of the optic disks in the presence of nystagmus on direct forward gaze. When the nystagmus has been abolished, it is possible to evaluate the visual acuity and thereby determine whether or not the clinical finding of pallor of the optic disks is of pathologic significance. The eye movements were recorded electrically in order to eliminate the deficiencies of observation with the naked eye and provide permanent records.

MATERIAL AND METHOD

Eight patients were studied. Seven had clinical evidence of multiple sclerosis. The eighth patient, whose condition was originally diagnosed as multiple sclerosis, proved to have an Arnold-Chiari malformation. All patients showed the combination of defective vision, oscillopsia, and

1. (a) Bender, M. B.: Effects of Barbiturates on Ocular Movements (Nystagmus), Confinia neurol. **7**:144-147, 1946. (b) Bender, M. B., and O'Brien, F. H.: Influence of Barbiturate on Various Forms of Nystagmus, Am. J. Ophth. **29**:1541-1552 (Dec.) 1946. (c) Bender, M. B., and Gorman, W. F.: Vertical Nystagmus on Direct Forward Gaze with Vertical Oscillopsia, ibid. **32**:967-972 (July) 1949. (d) Bender, M. B.; Nathanson, M., and Green, M.: Effects of Intravenous Tolserol on Normal and Abnormal Ocular Movements (Nystagmus), ibid. **34**:579-584 (April) 1951.

nystagmus on direct forward gaze, in addition to other signs of neural dysfunction. In four of these patients the pallor of the optic disks was of sufficient degree to be considered pathologic.

Tests of visual acuity were made prior to and after intravenous administration of amobarbital (amytal®) sodium. They consisted of the Snellen-chart and newspaper reading, starting with large headlines, then subheads, then standard body type. For five of the patients a special test was improvised, so that it could be employed easily during the administration of the drug and the simultaneous recording of the eye movements. For this test (Fig. 1) a milk-glass screen, 18 by 18 in. (45 by 45 cm.) was placed 4 ft. (120 cm.) away from the patient at eye level. On it was drawn a red circle around four large and small digits. The patient was asked to look straight ahead and report what he saw.

Recordings of the nystagmus were made using periorbital skin electrodes and four channels of a standard electroencephalograph, adjusted in such a way as to filter out almost all electrical activity except that caused by the eye movements (corneoretinal potential). This method, described before,[2] permits recording of the rate and character of eye movements that cannot be accurately perceived with the naked eye, determination of exact time relationships, and preservation of the data for future examination and comparison.

All the recordings illustrated were taken with the eyes in the position of direct forward gaze. Sample tracings of the nystagmus were taken, and the record was continued while the patient received amobarbital sodium intravenously.
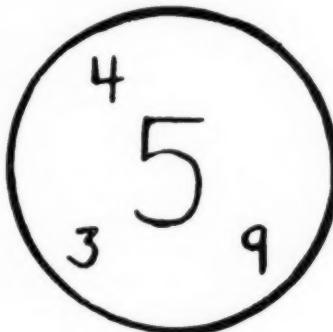
Fig. 1.—Test figure used in testing visual acuity.

The drug was given in dilute (2.5%) solution at the rate of 0.6 to 6.5 mg. per second, the total dose ranging from 50 to 150 mg. In no instance was the amount large enough to hinder mental functioning. All the subjects were able to carry out complicated commands and remained fully oriented.

The recording was continued about 20 minutes after the injection, and usually we were able to detect the early return of the nystagmus. The patients left for home approximately 45 minutes after the administration of the drug and were told to notify us when their vision returned to the previous degree of disturbance.

REPORT OF CASES

CASE 1.—The patient, who had multiple sclerosis, complained of "jumpy" and "blurring" vision of three years' duration.

In addition to other signs characteristic of multiple sclerosis, there was bilateral pallor of the optic disks. Accurate determination of visual fields was impossible, but on confrontation no localized defect could be elicited. She could read only large, bold print. She refused to read

2. Bergman, P. S.; Nathanson, M., and Bender, M. B.: Electrical Recordings of Normal and Abnormal Eye Movements Modified by Drugs, A. M. A. Arch. Neurol. & Psychiat. 67:357-374 (March) 1952.

smaller print or the Snellen chart because it was "annoying" to do so. There was a rapid horizontal and oblique nystagmus in all positions of the eyes, including direct forward gaze.

The electrical record revealed the nystagmus on direct forward gaze to have two components, regular sinusoidal waves at 4 cps, mixed irregularly with saw-toothed waves at 1.5 cps in all channels (Fig. 2). Twenty seconds after receiving 150 mg. of amobarbital sodium intravenously, she said, "Things are getting steady." Two minutes later the previous visual disturbances and the nystagmus were completely gone. She then was able to read standard newspaper type easily. The Snellen acuity was 20/50. The record showed only random eye movements. Periodic nystagmus was noted prior to her departure 40 minutes later, and, according to the patient's report, the visual disturbance returned to its previous state after three hours.

CASE 2.—The patient, who also presented all the clinical criteria for the diagnosis of multiple sclerosis, complained of "nearsightedness" in the right eye of three years' duration.

Examination revealed pallor of the right optic disk. The left optic disk appeared normal. When the left eye was covered, she described objects as "bobbing up and down" and could make out only large objects and headline-sized type. The Snellen acuity was 20/200 in the right eye, with normal vision in the left eye. A vertical pendular nystagmus, present in all directions of gaze, was noted in the right eye only. There was no nystagmus in the left eye in any position.

The electrical record of the nystagmus on direct forward gaze showed regular sinusoidal waves at 4 cps in the vertical plane of the right eye only (Fig. 3A).
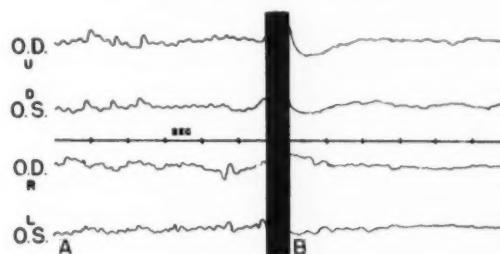
Fig. 2 (Case 1).—*A*, before amobarbital: The record shows regular, to-and-fro deflections at 4 cps, more marked in the vertical plane. In this plane slower (1.5 cps) saw-toothed deflections are superimposed. In the horizontal plane a few deflections faster than 4 cps are also present. *B*, after amobarbital: Irregular deflections of low amplitude, representing random movements, are present in all channels. The regular deflections of the previous nystagmus are no longer present.

In this and in all subsequent illustrations, the eye movements are represented as follows: The upper two lines record vertical movements of the right and left eyes respectively. Upward movement is represented by an upward deflection, and downward movement, by a downward deflection. In the lower two lines horizontal movement is recorded. Upward deflection represents movement to the right, and downward deflection, movement to the left. This and all subsequent records were made with the patient looking directly forward.

After receiving 150 mg. of amobarbital sodium, she spontaneously stated that everything was "still" and "clear." Forty seconds later no trace of nystagmus could be seen on the record (Fig. 3B). The visual acuity was now 20/50 in the right eye, and she was able to read newspaper body type with few errors. According to the patient's report, her visual disturbance did not return to its previous state until 24 hours later, although a slight vertical nystagmus could be seen reappearing in the right eye 30 minutes after the completion of the injection.

CASE 3.—The patient had multiple sclerosis of long standing and blurring of vision for 10 years.

Examination revealed pallor of both optic disks, more apparent on the right. The visual fields appeared normal on confrontation. In the test square she identified the circle and the number *5* but could not make out the smaller numbers. She made many errors on reading body

type. The Snellen acuity was 20/40 — 1. In further describing her visual defect, she said that the numbers and letters seemed to be moving, but she was not able to define this sensation more accurately.

Examination of the extraocular movements revealed a coarse vertical nystagmus, with a slight rotary component, on direct forward gaze. In addition, there was dissociated horizontal nystagmus (greater in the abducted eye) on each direction of lateral gaze, with coarse vertical nystagmus on upward and downward gaze. The record showed regular sinusoidal waves at 4 cps in all channels, with superimposed slower waves in the horizontal channels (Fig. 4).

After receiving 62.5 mg. of amobarbital sodium in 25 seconds, she spontaneously identified the numbers 9, 3, and 4 on the test glass (Fig. 1) and claimed that everything looked clear.
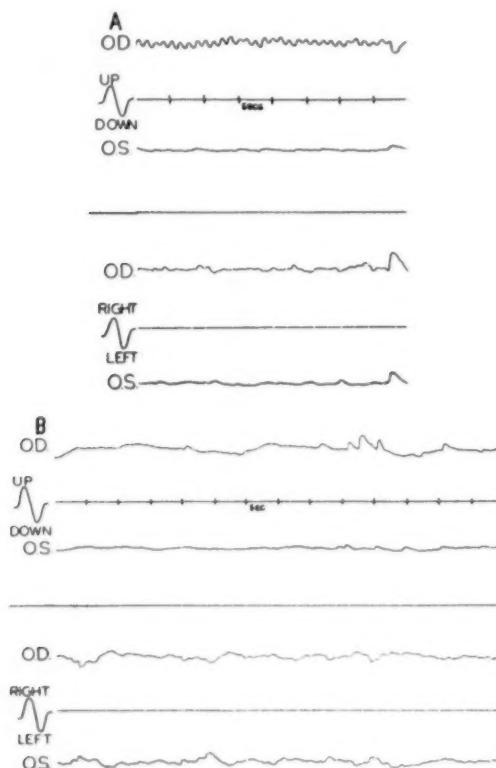
Fig. 3 (Case 2).—*A*, before amobarbital: There are regular 4-cps deflections in the vertical plane of the right eye only. *B*, after amobarbital: Only random movements are present. The rhythmic, 4-cps activity has disappeared. The 3-cps saw-toothed waves to the right of the record represent gaze nystagmus on inadvertent upward gaze.

Forty seconds later there was no evidence of nystagmus. Improvement in reading and in the Snellen chart score was noted. Nystagmus began to return intermittently 12 minutes later (Fig. 5), but the amplitude was lower than previously. The visual disturbances began to return in 22 minutes.

CASE 4.—The patient, with multiple sclerosis, complained of blurring of vision and oscillopsia in the horizontal plane of three years' duration.

Examination revealed bilateral pallor of the optic disk. No defect of the fields of vision could be demonstrated on gross testing. She could not identify anything in the test square,

although she stated that "something" was in the middle. She could read only large headline type. There was rapid horizontal nystagmus on direct forward and on lateral gaze, when it was more pronounced in the abducted eye (dissociation). An oblique nystagmus was noted on upward gaze.

The electrical recording with the eyes in the midposition showed sinusoidal waves at 4 cps in the horizontal plane, more pronounced in the right eye (Fig. 6, 1).

When the patient had received 100 mg. of amobarbital sodium in 160 seconds, she reported spontaneously that she saw the circle and exclaimed, "Things are positively still!" Thirty seconds later she stated that something else was in the circle, but she could not identify it. She was then able to read subheads, with few errors. No nystagmus could be detected at this time. When, 20 seconds later, the experiment was discontinued, there still was no return of the nystagmus. The patient reported that the visual disturbance returned to its former state the next morning.

CASE 5.—The patient complained of blurring of vision in both eyes of four years' duration. After further questioning, he said that objects appeared to be constantly moving up and down.

Examination revealed normal ocular fundi and visual fields. He was unable to read newspaper body type. The Snellen acuity was 20/200.
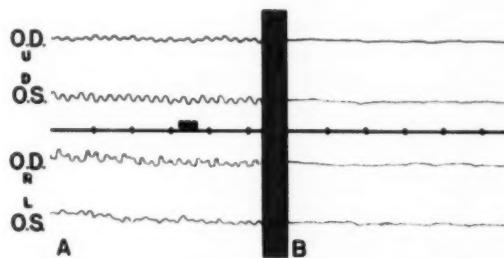
Fig. 4 (Case 3).—*A*, before amobarbital: Sinusoidal waves at 4 cps appear in all channels, and slower saw-toothed deflections are superimposed in the horizontal channels. *B*, after amobarbital: The record is essentially flat.

Fig. 5 (Case 3).—The vertical channel of the right eye shows sporadic return of nystagmus 12 minutes after administration of amobarbital sodium. The former 4-cps activity appears intermittently and at low amplitude.

Nystagmus appeared on the record as regular sinusoidal waves at 5 cps, of the same frequency in the two eyes, and more apparent in the vertical channels (Fig. 6, 2).

After receiving 100 mg. of amobarbital sodium, he reported that the "shaking" had stopped. Five seconds later no trace of the nystagmus could be detected. He was then able to read newspaper body type, and the Snellen acuity was 20/40. This effect lasted 16 minutes and thereafter fluctuated. The nystagmus and oscillopsia returned to their previous state in 40 minutes.

CASE 6.—The patient, a woman with multiple sclerosis, complained of blurring of vision in both eyes, more pronounced on the left, of seven years' duration. She denied having oscillopsia.

Examination revealed that the fundi and fields of vision were normal. The Snellen chart reading was 20/70 in the left eye and 20/50 in the right eye. Although she was able to make out several words of body type, she said the blurring was so disturbing that she refused to continue. A coarse vertical nystagmus was noted on direct forward and upward gaze. On lateral gaze to either side it became oblique.

The electrical record with the eyes in direct forward gaze showed slow regular saw-toothed waves in the vertical plane of each eye at 1 to 2 cps (Fig. 6, 3). Three minutes 40 seconds after completion of the intravenous injection of 150 mg. of amobarbital sodium, the patient reported

that the blurring was no longer present. Thirty seconds later no evidence of the nystagmus could be detected in the record. She was then able to read newspaper print The Snellen chart reading was 20/40 in the left eye and 20/30 in the right eye. The visual disturbance returned three hours later, but the nystagmus reappeared periodically at the end of 14 minutes.

CASE 7.—The patient, with a condition diagnosed as multiple sclerosis, complained of blurring of vision and "shaking of the eyes" of five years' duration. He also described oscillopsia in the horizontal plane, saying, "Everything jumps from side to side."

Examination revealed normal fundi and visual fields. He could make out an occasional word of body type. The Snellen chart reading was 20/200 for each eye. In the test square he was able to identify the circle only. There was a fine rapid horizontal nystagmus in all directions of gaze, including direct forward gaze.

The record showed regular sinusoidal waves at 5 cps in the horizontal plane (Fig. 6,4). After he received 50 mg. of amobarbital sodium in 15 seconds, he spontaneously called out, "I see number 5—everything is clear!" The nystagmus was greatly reduced in amplitude at that time, and five minutes later it was completely gone. He was able to identify the 4 and 9, to read standard body type fluently, and to read the Snellen chart at 20/50 + 2.

The nystagmus began to return in short runs within 10 minutes, but "steady vision" persisted for six hours, according to the patient's report.
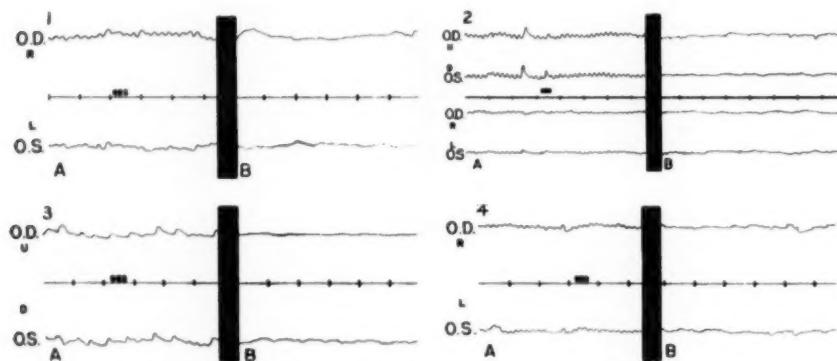
Fig. 6.—1 (Case 4), (A) before amobarbital: Horizontal channels only. There are sinusoidal waves at 4 cps, more marked in the right eye. (B) after amobarbital: Slow random eye movements are recorded. The rhythmic activity has disappeared.

2 (Case 5), (A) before amobarbital: Regular sinusoidal waves appear in all channels at 5 cps, more marked in the vertical channels but equal in the two eyes. (B) after amobarbital: The former rhythmic activity has disappeared, leaving only sporadic eye movements.

3 (Case 6), (A) before amobarbital: Vertical channels only. There are somewhat irregular saw-toothed waves at the rate of 2 cps. (B) after amobarbital: The electrical record is almost flat, indicating the absence of nystagmus.

4 (Case 7), horizontal channels only. (A) before amobarbital. There are regular sinusoidal waves at 5 cps in both eyes. (B) after amobarbital: Rhythmic activity has disappeared, and only random eye movement is recorded.

CASE 8.—A man aged 28 had had blurring of vision and diplopia at a distance for the past 18 months. He claimed that by holding his head forward, thus keeping his eyes up, he was able to see things "clear and steady," but that when his head was straight up or back, so that his eyes were in the midposition or down, "things begin to jump up and down." X-rays of the base of the skull and myelograms revealed platybasia and herniation of the cerebellar tonsils, typical of the Arnold-Chiari malformation, a diagnosis subsequently confirmed at operation. The patient characteristically held his head tilted forward, so that his eyes were in relative upward gaze. In this position no nystagmus was noted and his vision was normal. When the eyes were in the midposition and the head was erect, there was a coarse vertical nystagmus, and

he complained of oscillopsia. He was unable to read large newspaper type and could not identify any numbers in the test circle. The vision and the nystagmus were worse when the eyes were in the position of downward gaze. In addition, a coarse oblique nystagmus was present on lateral gaze to either side with the head in any position.

The record (Fig. 7) showed that on direct forward and downward gaze there were regular 3-cps saw-toothed waves; on upward gaze no nystagmus was apparent.

After 150 mg. of amobarbital sodium was injected, in two minutes, the nystagmus was abolished on direct forward gaze and was unchanged on downward gaze, and a typical barbiturate nystagmus then appeared when he looked upward. Tests for visual acuity on direct forward gaze (head erect) showed that he was able to read all the figures in the test circle with ease and read standard newspaper body type fluently. The effect of the drug wore off in approximately 30 minutes, with return of the nystagmus and the associated visual defects.

COMMENT

From the foregoing observations it is evident that nystagmus on direct forward gaze played an important role in producing the visual disturbances of these patients. The improvement in visual acuity that took place concomitantly with abolition or alteration of the nystagmus by intravenous administration of barbiturates clearly demonstrated this point. The electrical recording of the eye movements showed
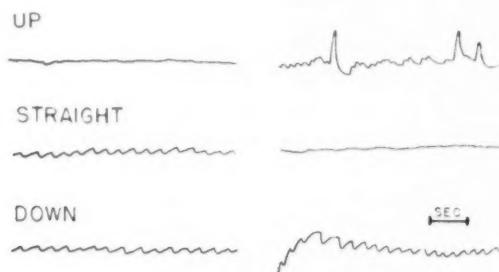
Fig. 7 (Case 8).—Left, before amobarbital: The record is flat when the patient looks upward. When he looks straight ahead or downward, there are regular saw-toothed deflections at 3 cps. This represents jerky nystagmus, with the fast component directed downward. Right, after amobarbital: On upward gaze, regular saw-toothed deflections at 5 cps are present, with the fast component directed upward. This represents typical gaze nystagmus due to amobarbital. The large spike-like deflections represent eye blinks. On direct forward gaze ("straight") the record is flat, indicating the cessation of the nystagmus previously present. On downward gaze there is no essential change from the behavior prior to injection of amobarbital.

In order that all the phenomena may be depicted in one illustration, only tracings of vertical movements in the right eye were used. The record of the left eye, not illustrated, was identical.

for the first time that all that was necessary for the disappearance of the oscillopsia was a change in the character of the nystagmus. The complete cessation of the nystagmus always lagged behind the improvement in visual acuity; when the effect of the drug wore off, the nystagmus returned first, usually in short runs of lower amplitude, but the complaint of oscillopsia or blurred vision did not reappear until the nystagmus became continuous at its previous rate and character.

To what extent pallor of the optic disks in the presence of nystagmus on direct forward gaze produces visual disturbances can be determined only by abolishing the nystagmus and comparing the visual acuity before and after. The frequently equivocal clinical impression of "optic pallor," or "temporal pallor," may prove not to be of pathologic significance.

The visual acuity of several patients with optic nerve atrophy who had no evidence of abnormal ocular movements on direct forward gaze was not measurably improved after intravenous injection of amobarbital sodium.

Brickner,[3] in 1936, called attention to the symptom of oscillopsia in patients with multiple sclerosis. A more recent study of ocular disturbances in multiple sclerosis [4] led to the following statements:

This [oscillopsia] may be the result of partial atrophy of the optic nerve. . . . Ocular nystagmus impairs central visual acuity, but the acquired nystagmus of multiple sclerosis does not affect central visual acuity to any appreciable amount.

However, there is considerable collateral evidence to show that nystagmus and poor vision are more than casually related; patients who have sporadic nystagmus complain of oscillopsia only when the nystagmus is present; nystagmus induced in normal persons by caloric stimulation of the ears or by rotation is often associated with oscillopsia; latent nystagmus (a congenital defect brought on by covering one eye or otherwise interfering with binocular fixation) produces oscillopsia or blurred vision only when the eye is oscillating; normal subjects with voluntary nystagmus describe oscillopsia while inducing their nystagmus, but not at other times; vertical and horizontal nystagmus leads to vertical and horizontal oscillopsia respectively. We have confirmed these observations, and the results of this study are consistent with this point of view.

There remains the problem of the relation of the so-called physiological nystagmus to visual acuity. Because visual acuity cannot be explained solely upon the anatomical distribution of retinal receptors, it has been suggested that the fine rapid to-and-fro movements of the eyes, known as physiological nystagmus, which occur on fixation in normal subjects act to scan the visual field and thus expose adjacent retinal cells to the same point. In detailed studies of physiological nystagmus, however,[5] it was shown not only that the movements were too small to provide the postulated scanning but that the visual acuity actually declined when the nystagmus was most prominent and improved when the movements became imperceptible. It appears from these studies that fixation nystagmus of any type decreases visual acuity. Unfortunately, it is not possible to study each subject under conditions in which the nystagmus is present or absent.

The nystagmus on lateral and vertical gaze produced by amobarbital sodium is rarely responsible for complaints of disturbed visual acuity, since only the mid-position of the eyes is involved in useful vision.

Previously it was reported [1d] that intravenous injections of mephenesin (tolserol®) has similar effects on eye movements. The only difference noted was that mephenesin induced a greater degree of fluctuation. Alcohol administered intravenously abolished fixation nystagmus and the concomitant oscillopsia in two patients reported by Bender and Gorman.[1e] While these drugs are effective when

3. Brickner, R. M.: Oscillopsia: A New Symptom Commonly Occurring in Multiple Sclerosis, Arch. Neurol. & Psychiat. 36:586-589 (Sept.) 1936.

4. Yaskin, J. C.; Spaeth, E. B., and Vernlund, R. J.: Ocular Manifestations of 100 Consecutive Cases of Multiple Sclerosis, Am. J. Ophth. 34:687-697 (May, Pt. 1) 1951.

5. Ratliff, F., and Riggs, L. A.: Involuntary Movements of the Eye During Monocular Fixation, J. Exper. Psychol. 40:687-701, 1950. Barlow, H. B.: Eye Movements During Fixation, J. Physiol. 116:290-306 (March) 1952. Ratliff, F.: The Role of Physiological Nystagmus in Monocular Acuity, J. Exper. Psychol. 43:163-172, 1952.

injected intravenously, they do not seem to influence the nystagmus when the same amount of drug is ingested by mouth. It must be emphasized again that the amount of amobarbital sodium given intravenously to our patients did not produce a marked change in consciousness or affect their mental alertness to any significant degree. Two patients, not included in this series, who were given large doses of amobarbital sodium and mephenesin by mouth, did not show such a change in the character of the central nystagmus or the oscillopsia. From this it follows that a known barbiturate given in such a way as to eliminate side-effects, or a new drug without such side-reactions, may some day prove capable of correcting these visual disturbances when given by mouth in clinically feasible doses.

SUMMARY

1. Intravenous administration of amobarbital (amytal*) abolished nystagmus on direct forward gaze and the associated blurring of vision and/or oscillopsia in eight cases of neurologic disorders.

2. The pallor of the optic disk present in four of the patients proved not to be the sole cause of their visual disturbance, since they, too, showed definite improvement in visual acuity when the fixation nystagmus was abolished.

3. The patient's spontaneous report of improved vision always occurred just prior to the cessation of the nystagmus. Apparently all that was necessary, according to the records, was a change in the amplitude or other characteristics of the nystagmus.

The return of the nystagmus preceded the return of the visual disturbances and was characterized by fluctuation.

4. In evaluating the visual disturbances in patients with multiple sclerosis, it is important to consider not only the condition of the optic nerves but the presence or absence of nystagmus on direct forward gaze. Intravenous injection of amobarbital sodium is useful in making this evaluation.

INTELLECTUAL FUNCTIONS IN MYXEDEMA

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AMONG the earliest reports linking athyreosis in adulthood to changes in mental functioning are those of Blaise [1] and White.[2] Since those reports a number of papers have appeared citing instances of mild and severe mental breakdown and neurotic and psychotic development associated with myxedema. Writing in 1944, Zondek and Wolfsohn [3] reported:

> The most impressive association of mental and endocrine affections . . . is encountered in hypothyroid patients. . . . So far no definite myxœdema psychosis has been established, but slowness and slackness of mental reactions, and a lack of emotional response which may amount to complete lethargy, are obvious in almost every case.

They described an instance of a 23-year-old woman with myxedema of 18 months' duration who showed mental changes characteristic of schizophrenia (hallucinatory psychosis). With treatment for hypothyroidism, this patient recovered completely from the psychological disturbance in two weeks. Zondek and Wolfsohn expressed the belief that the improvement was due to dehydration of cerebral tissues. Hayward and Woods [4] included among the psychological effects of hypothyroidism the following: slowing of intellect, intense fear, restlessness, hallucinations and delusions, depression, irritability, and excitement. Stoll [5] reported that personality changes accompanying myxedema are characterized by irritability, untruthfulness, suspicion, delusions, retarded cerebration, inability to concentrate, introversion, failing memory, and slowness of speech and motility. Ziegler,[6] in considering the wide range of psychological symptoms that are encountered, proposed that the individual picture may be an accentuation or exaggeration of the characteristic behavioral predisposition of the patient. The myxedematous state precipitates the psychotic symptoms, which

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1. Blaise, H.: De la cachexie pachydermique (myxoedème des auteurs anglais) : Observation nouvelle avec aliénation mental transitoire, Arch. neurol. **3**:60 and 141, 1882.

2. White, E. W.: A Case of Myxoedema Associated with Insanity, Lancet **1**:974 (May) 1884.

3. Zondek, H., and Wolfsohn, G.: Myxœdema and Psychosis, Lancet **2**:438 (Sept. 30) 1944.

4. Hayward, E. P., and Woods, A. H.: Mental Derangements in Hypothyroidism: Their Misleading Effects in Diagnosis, J. A. M. A. **97**:164 (July 18) 1931.

5. Stoll, H. F.: Chronic Invalidism with Marked Personality Changes Due to Myxedema, Ann. Int. Med. **6**:806 (Dec.) 1932.

6. Ziegler, L. H.: Myxedema and Psychosis, Proc. Staff Meet., Mayo Clin. **5**:141 (May 21) 1930.

subside with thyroid treatment. These reports and others have been a sufficient basis for writers of textbooks [7] to include statements of which the following is perhaps typical:

Patients with myxœdema become slow in both physical movements and cerebration. Psychoses with schizophrenic tendencies are not uncommon. They lose their memory and suffer from apathy and somnolence.[8]

While most writers on the psychiatric conditions associated with myxedema have postulated lowered cerebral metabolism and edema as likely organic bases for the mental changes, there have been some neurophysiological and neuropathological studies directed toward the specification of these organic changes. Uyematsu [9] did a thorough autopsy on a 65-year-old woman who died after 10 years of typical myxedematous symptoms. He found pathological changes in the brain and cerebellum consisting of arteriosclerotic changes, general senile changes, and cell changes associated with the edematous condition. Uyematsu believed that these changes were due to the effects of myxedema and that the cell changes associated with the edematous condition were pathognomonic.

Scheinberg and Stead [10] measured cerebral blood flow and metabolism by means of the nitrous oxide technique in a group of nine hyperthyroid subjects and eight myxedematous subjects. Although they had found increased cardiac output and splanchnic oxygen consumption in a previous series of hyperthyroid subjects, none of the measures of cerebral metabolism functions in this group differed significantly from normal. The myxedematous subjects gave strikingly different results. Three of the eight subjects were studied both before and after treatment. The authors stated: [The myxedematous patients]

showed reductions in cerebral blood flow (38%) and oxygen consumption (27%) commensurate with the fall in cardiac output and total oxygen consumption that is known to occur in these patients. Cerebral glucose consumption decreased in proportion to the decrease in cerebral oxygen consumption. Cerebral vascular resistance was increased almost 100%, and definitely decreased following treatment. The cerebral metabolic functions returned toward normal, in conjunction with clinical improvement, in the three patients restudied after thyroid therapy. These data indicate that in hyperthyroidism the brain does not share in the general increase which occurs in body metabolism, and that the clinical signs of mental dysfunction so commonly observed in myxedema may be accounted for by the decreased cerebral metabolism in this disease.

The impressionistic observations of intellectual slowing and personality changes, together with the evidence of possible neuropathology and cerebral metabolic impairment in myxedema, constitute an adequate basis for the hypothesis that such changes may be reflected in quantitative terms by valid and sensitive tests of intelligence and personality. A survey of the literature reveals that very little has been done in the way of quantitative measurement of psychological functions in myxedematous patients.

7. Means, J. H.: The Thyroid and Its Diseases, Ed. 2, Philadelphia, J. B. Lippincott Company, 1948. McGavack, T. H.: The Thyroid, St. Louis, C. V. Mosby Company, 1951.

8. Conybeare, J. J., editor: Textbook of Medicine, Ed. 9, Edinburgh, E. & S. Livingstone, 1949, p. 214.

9. Uyematsu, S.: A Case of Myxedematous Psychosis: Clinical and Pathologic Report, Arch. Neurol. & Psychiat. 3:252 (March) 1920.

10. Scheinberg, P., and Stead, E. A., Jr.: Cerebral Metabolism in Hyperthyroidism and Myxedema, Federation Proc. 9:113 (March) 1950.

Blumgart and Davis [11] reported a study of the effects of complete removal of the thyroid gland in the treatment of chronic heart disease. Many of their patients had no untoward postoperative symptoms of myxedema because small doses of thyroid were given when necessary. They reported no quantitative results of psychological testing which would permit an assessment of the statistical significance of preoperative and postoperative results and, further, made no mention of the use of a control group, which would have been desirable in a study such as this. They reported, however, that, while speech was slowed, the results on psychological testing showed no impairment in mental acuity in these patients, in whom the myxedematous state was controlled.

Several instances of psychological measurements on hypothyroid subjects have been reported. Viamonte Cuervo [12] described the case of a 19-year-old youth with advanced hypothyroidism who attained a mental age of 10 years 11 months. Wheeler [13] has given pretreatment and post-treatment results for a boy who was first tested when he was 12 years old. His intelligence quotient at this time was 67. With thyroid treatment there was marked improvement in his general physical growth rate. He was tested again at the age of 14, when the intelligence quotient was 86. It would appear from these results that hypothyroidism, at least in the period of physical growth and development, may measurably impair intellectual development. These results, of course, do not seem surprising in the light of our long-standing familiarity with the physical and psychological findings in cretinism.

Gantt and Fleischmann [14] reported the results of an experiment which are to some extent in disagreement with those cited above. They examined a 13-year-old hypothyroid boy over a two-year period during which he was receiving thyroid treatment and found that the intelligence quotient showed a "marked stability." They explained this result by pointing out that the intelligence quotient depends largely upon an accumulation of learning, and that a method sensitive to the immediate condition of the subject is necessary. [Their attempt to measure]

higher nervous activity by the conditional reflex method showed that the ability to form and differentiate conditional reflexes ran parallel to the metabolic records (BMR, serum cholesterol) and to the EEG, [which] showed a marked improvement with several weeks after thyroid therapy, the improvement in these items reaching a level in two months, without further change after two years of therapy.

A possible basis of explanation for the disparity between the findings of Gantt and Fleischmann and those of Wheeler in regard to the intelligence quotient may be suggested by certain experiments with animals. Scow [15] studied maze learning in

11. Blumgart, H. L., and Davis, D.: Hypothyroidism Induced by Complete Removal of the Normal Thyroid Gland in the Treatment of Chronic Heart Disease, Endocrinology **18**:693 (Nov.-Dec.) 1934.

12. Viamonte Cuervo, L.: Retraso mental, hipotiroidismo, bocio coloide, Rev. cien. méd. **2**:103 (April) 1939.

13. Wheeler, R. H.: The Science of Psychology: An Introductory Study, Ed. 2, New York, Thomas Y. Crowell Company, 1940.

14. Gantt, W. H., and Fleischmann, W.: Effect of Thyroid Therapy on the Conditional Reflex Function in Hypothyroidism, Am. J. Psychiat. **104**:673 (May) 1948.

15. Scow, R. O.: The Retarding Effect of Allyl Thiourea and of Partial Thyroidectomy at Birth upon Learning in the Rat, J. Comp. Psychol. **39**:359 (Dec.) 1946.

rats subjected to thyroidectomy at birth and found that they made more errors than did normal rats. Brady [16] made the same type of study with thyroidectomized adult rats and found no significant differences from the maze performance of normal rats. These two studies, then, would suggest that thyroid dysfunction prior to physical maturation causes psychological impairment. Not enough information about the duration of hypothyroidism in Wheeler's and Gantt and Fleischmann's subjects was given, but this factor may be the explanation for the different findings regarding the intelligence quotient.

In spite of the frequently encountered statements of impaired intellectual functions in myxedema, there appears to be an almost complete absence of reported results of measurement with psychological tests of intelligence.

MATERIAL AND METHODS

Problem.—The problem in the present study was to investigate the intellectual functions in a group of adults with myxedema to determine whether measureable impairment was reflected by the Rorschach test.

TABLE 1.—*Distribution Constants for Three Equated Groups*

Group	No.	Age	Education	I. Q.
Neurosis	15			
Mean		43.53	10.53	91.47
S. D.		8.90	2.85	20.18
Myxedema	15			
Mean		43.93	9.40	92.53
S. D.		10.13	3.07	19.58
Organic brain damage	15			
Mean		40.47	10.40	89.67
S. D.		9.25	3.01	18.44

Population.—Three groups were used, each composed of 15 subjects. As a basis for comparing the Rorschach test results of the myxedematous subjects, the members of this group were matched individually with neurotic and brain-damaged subjects on the basis of sex, chronological age, number of completed years of formal academic education, and intelligence quotient, as measured by the Henmon-Nelson test of mental ability. Each group was composed of 11 women and 4 men. The means and standard deviations for each of the equated variables are presented in Table 1.

The diagnostic classifications of the patients in the neurotic group were as follows: depression, 10; anxiety neurosis, 2; obsessive-compulsive neurosis, 1; alcoholism without deterioration, 1, and simple schizophrenia, 1. The large proportion of depressed patients were included as a conservative procedure. It was felt that they would resemble the myxedematous subjects in their slowness of reaction and thus deemphasize the possibility of obtaining results of significance only to these two specific groups of patients. The remainder of the subjects, particularly the schizophrenic patient, were selected to give the group more heterogeneity. In the group with organic brain damage only those subjects were included who gave definite evidence of organic cerebral damage and/or dysfunction. The group included seven persons with surgical removal of brain tumors, three with degenerative vascular changes, two with cerebrovascular accidents, two with epilepsy, and one with a frontal gyrectomy. A thorough endocrinological examination was made of each patient classified as myxedematous. A few patients were tested

16. Brady, E. B.: The Influence of Thyroidectomy and Thyroxin Injection on the Maze Behavior of Adult Rats, J. Comp. Psychol. **34**:213 (Oct.) 1942.

psychologically very shortly after thyroid treatment was initiated, but usually the tests were made before the treatment was begun. The duration of hypothyroidism of the myxedematous patients before treatment, as well as the severity of symptoms, was variable.

Procedure.—As only 18 subjects composed the myxedematous group, it was felt necessary to use matched groups of neurotic subjects and subjects with organic brain damage for inter-group comparisons. The neurotic subjects theoretically show no impairment of intellectual functions as a result of organic brain dysfunction, although they have many personality disturbances similar to those often attributed to persons with myxedema. The group with organic brain damage should show distinct impairment of intellectual functions, in line with previous reports of measurements with the Rorschach test [17]; judging from the literature, the myxedematous subjects may also have organically impaired intellectual functions. This experimental design, then, should have the advantage of at least partially disclosing the extent to which myxedematous patients suffer organically impaired intelligence (their similarity to brain-damaged subjects) and/or personality disturbances (their similarity to neurotic subjects). This investigation does not inquire regarding possible effects of sex, age, education, and intelligence quotient, and therefore these variables are controlled by equation in the three groups. Previous studies [18] have suggested that the intelligence quotient does not necessarily show any systematic variation with organic brain damage. It may be of interest in some future study to permit these factors to vary systematically in an attempt to determine their possible significance.

The Rorschach test was administered to each of the subjects individually and the scoring completed before any of the groups were composed or the subjects matched on the controlled variables. The means and standard deviations for the quantitatively scored Rorschach test variables were calculated. Intergroup statistical comparisons of the means were made by use of Student's *t* technique. As another approach to quantitative differentiation of the three groups, the frequencies with which Rorschach test scores of members of one group exceeded the scores of the paired subjects in the other groups were enumerated and the frequency differences tested for significance by use of chi-square with Yates's correction for continuity. Finally, chi-square comparisons of the frequency of occurrence of various Rorschach test "signs" of organically impaired cerebral function were made.

RESULTS AND COMMENT

The Rorschach test means and standard deviations for the three groups are presented in Table 2.

Rather than attempt to get an over-all view of the comparative performance of the three groups from Table 2, it would be advantageous to pass directly to Chart 1, which presents the means for each group in graphic form. In construction of the Chart, the scores for the members of each of the groups were combined for each variable, and a *t*-score scale was constructed which corresponded to the raw scores. The means for each group were then indicated in accordance with the *t*-score scale

17. (*a*) Aita, J. A.; Reitan, R. M., and Ruth, J. M.: Rorschach's Test as a Diagnostic Aid in Brain Injury, Am. J. Psychiat. **103**:770 (May) 1947. (*b*) Reitan, R. M.: Relationships of Certain Rorschach Test Variables to the Abstraction and Power Factors of Biological Intelligence, Thesis, University of Chicago, 1950; (*c*) Performance of Aphasic, Non-Aphasic, and Control Subjects on the Rorschach Test, J. Gen. Psychol., to be published; (*d*) Intellectual Functions of Aphasic and Non-Aphasic Brain Injured Subjects, Neurology, to be published. (*e*) Piotrowski, Z.: On the Rorschach Method and Its Application to Organic Disturbances of the Central Nervous System, Rorschach Res. Exchange **1**:23 (Nov.) 1937; (*f*) Rorschach Ink-Blot Method in Organic Disturbances of Central Nervous System, J. Nerv. & Ment. Dis. **86**:525 (Nov.) 1937. (*g*) Harrower-Erickson, M. R.: Personality Changes Accompanying Cerebral Lesions: Rorschach Studies of Patients with Cerebral Tumors, Arch. Neurol. & Psychiat. **43**:859 (May) 1940.

18. Hebb, D. O.: Intelligence in Man After Large Removals of Cerebral Tissue: Report of 4 Left Frontal Lobe Cases, J. Gen. Psychol. **21**:73 (July) 1939.

TABLE 2.—*Distribution Constants for Three Diagnostic Groups on Rorschach Test Variables*

	R	W	D	Dd	M	Sum C	Z	F+	F-	Total F	CF	FC	Total C	YP	FY	Total Y	FV	Total V	S	P	T/R	Z T/R	Z Z/R
Neurosis																							
Mean	33.75	9.20	20.08	4.47	2.07	5.60	41.22	13.54	3.67	18.81	3.60	2.40	6.54	1.20	4.00	5.40	1.07	1.13	3.20	7.00	48.02	1.25	1.43
S. D.	19.95	6.86	13.14	7.08	1.88	3.36	23.63	9.58	3.24	14.92	2.39	1.67	3.56	1.94	2.92	4.38	1.06	1.09	2.59	2.61	21.45	1.43	0.78
Myxedema																							
Mean	23.40	7.33	15.27	0.80	2.87	3.67	35.10	8.53	1.93	11.13	2.33	2.33	4.73	1.00	2.93	4.00	0.80	0.93	2.27	7.60	68.37	0.64	1.59
S. D.	10.11	3.32	9.34	1.76	3.08	1.91	13.39	3.46	1.29	5.18	1.81	1.96	2.65	0.97	2.30	2.48	1.22	1.53	2.24	1.78	39.30	0.35	0.49
Organic brain damage																							
Mean	19.13	6.20	11.47	1.47	1.47	2.63	24.25	8.27	3.13	12.14	1.33	1.33	3.07	0.18	1.80	1.93	0.27	0.27	0.80	5.54	39.96	0.49	1.28
S. D.	11.12	3.87	6.77	2.00	1.54	3.11	18.39	4.80	1.92	6.33	2.03	1.02	3.48	0.34	1.42	1.57	0.57	0.57	1.38	1.39	19.64	0.38	0.59

shown along the ordinate. The procedure in converting raw scores to standard scores has the advantage for graphic presentation of putting the results for successive variables on the same scale.

Four graphs are included in Chart 1 for ease of intergroup comparison. *A* presents the results for the neurosis and organic brain damage groups; *B*, the results for the myxedema and brain-damage groups; *C*, the results for the neurosis and myxedema groups, and *D*, the results for all the groups. It is obvious that the quantitative scores for the neurosis group consistently excel those of the brain-damage group. The same is true generally in comparing the myxedema and the brain-damage group, although the differences are not as prominent. *C* shows that
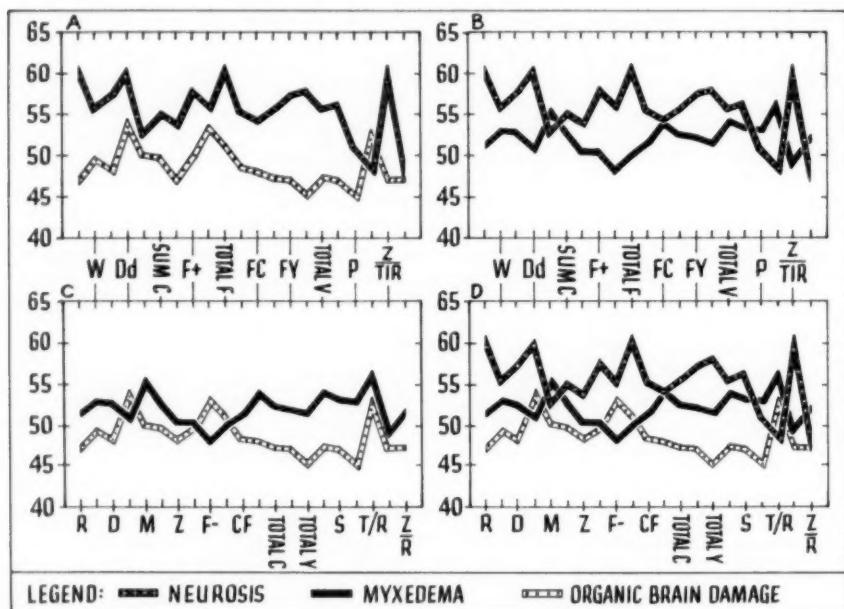
Chart 1.—Graphic presentation of mean Rorschach test scores converted to *t* scores for each of three diagnostic groups.

the scores for the neurosis group also excel the scores for the myxedema group, but the differences are not as large as in those for the neurosis and organic brain-damage groups. *D*, of course, summarizes the values shown by the other three graphs by presenting the results for all three groups. The trend in these graphs suggests strongly that a significant difference is present in the quantitative Rorschach test results for these three groups. The scores for the myxedematous subjects very consistently fall between those for the neurotic and those for the brain-damaged subjects.

Table 3 presents the *t* ratios, which provide a basis for determining the statistical probability, or level of confidence, that the obtained mean differences among the groups are other than sampling errors.

TABLE 3.—*Comparison of Mean Differences in Rorschach Test Variables for Three Diagnostic Groups by Means of t Ratios*

Groups	R	W	D	Det	M	Sum C	Z	F+	F-	Total F	CF	FC	Total C	FY	Total Y	Total V	S	P	T/R	Z T/R	Z Z/R
Neurosis vs. myxedema......	1.78	0.79	1.26	1.83	1.18	1.71	0.72	1.87	1.86	1.82	1.35	0.11	1.52	0.98	1.00	0.37	1.07	0.75	1.97	1.49	0.53
Neurosis vs. organic brain damage......	2.55	1.41	2.32	1.60	1.71	3.71	2.22	1.81	0.65	1.63	3.98	1.88	3.77	2.65	2.94	2.69	3.48	1.60	1.68	2.05	0.65
Myxedema vs. organic brain damage......	1.13	0.69	1.42	0.99	2.22	1.00	1.77	0.19	1.86	0.47	0.94	2.70	1.57	1.96	2.69	1.47	2.13	2.31	0.64	1.00	1.98

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For 14 degrees of freedom, a t value of 2.97 is needed to reach the 0.01 level of confidence, of 2.62 to reach the 0.02 level, and of 2.15 to reach the 0.05 level. In spite of the marked tendency of the scores of the myxedematous subjects to be lower than those of the neurotic subjects, as indicated in Chart 1, none of the specific comparisons of these two groups reach the 0.05 level of confidence. Comparison of the scores for the myxedema and those for the brain-damage group, in which the mean for the myxedema group is generally the higher, indicates several significant differences. The number of M (human movement) responses is greater for the myxedematous patients (0.02 level), as well as the number of form-color responses and the total number of responses involving surface shading, both of which exceed the 0.05 level. The greatest number of statistically significant differences occur in comparisons of the neurosis and the organic brain-damage group, as would be expected from Chart 1. Here, 10 of the 21 t ratios exceed the 0.05 level of confidence, and 4 of these are beyond the 0.01 level.

It is interesting to note particularly that the time per response was longer for the myxedema group, and that the average percentage of "good" form $(F+)$ responses was higher than that for either of the other groups. These results, while not statistically significant for the number of subjects used, tend to corroborate the commonly cited clinical impression of mental and verbal slowness in myxedematous persons and to indicate that these patients, if given enough time, are generally accurate in the information they supply.

From the results presented in Table 3, it would appear that the Rorschach test reflects no specific impairment of intellectual function in myxedema, but the trend of diminished associative ability shown in Chart 1 suggests that there is a generalized suppression of intellectual functions in myxedema which would become significant statistically if the groups were larger.

As another approach to possible differentiation of the quantitative results for the three groups, the number of subjects in one group whose scores exceeded those for the matched subjects in another group were determined for each variable: For example, the number of neurotic subjects who had a greater number of responses (R) than did the matched myxedematous subjects were counted, and vice versa. Chi-square was then used to determine the significance of group differences. The comparisons in which the chi-square values reached significance at the 0.01 and 0.05 levels of confidence are indicated in Table 4.

Generally, these results are similar to those indicated in the table of t ratios comparing the means for the three groups. In Table 4 the majority of significant differences are present in the comparisons of the neurotic and the brain-damaged groups. A number of significant differences are also found in favor of the myxedematous subjects when they are compared with the brain-damaged group. The only difference between the neurotic and the myxedematous subjects significant at the 0.01 level is $\frac{Z}{T/R}$ (speed of organizing), and this is primarily a reflection of the long response time of the myxedematous subjects.

The Rorschach test records in the three groups were also studied with reference to the frequency of occurrence of various "signs" of psychological dysfunction due to organic brain disturbances. Fourteen signs were used, 5 of the 10 that were proposed by Piotrowski,[17e,f] and 9 that were proposed by Aita, Reitan, and Ruth.[17a] Each of these 14 signs had previously been found to help in differentiating brain-injured

TABLE 4.—*Results of Chi-Square Tests of Frequency with Which Scores of Members of One Group Significantly Exceeded Scores of Paired Subjects in Another Group*

Groups	Confidence Level	R	W	Del	M	Z	$\frac{Z}{T:R}$	$\frac{Z}{R}$	F+%	F−	A%	S	Sum C	OF	FC	Total C	YF	FV	Total Y	FV	Total
Neurosis > organic brain damage	0.01	x	··	··	··	x	x	··	··	··	··	x	x	x	x	x	x	··	x	x	10
	0.05	··	x	··	··	··	··	··	x	··	··	··	··	x	··	··	··	x	··	··	4
Myxedema > organic brain damage	0.01	··	··	··	x	x	··	··	··	··	··	x	··	x	x	x	x	··	··	··	5
	0.05	··	··	··	··	··	··	··	x	··	··	··	··	··	··	··	··	··	··	··	8
Myxedema < organic brain damage	0.01	··	··	··	··	··	··	··	··	x	··	··	··	··	··	··	··	··	··	··	1
	0.05	··	··	··	··	··	··	··	··	x	··	··	··	··	··	··	··	··	··	··	1
Neurosis > myxedema	0.05	··	··	x	··	··	x	··	··	··	··	··	··	··	··	··	··	··	··	··	1
Neurosis < myxedema	0.05	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	··	1

from control patients. Their relevance to intellectual functions dependent upon the organic condition of the cerebrum is further indicated by their demonstrated relationship to Halstead's [19] measures of biological intelligence.[17b]

Chart 2 presents a graphic comparison of the relative frequency with which the signs occurred in each group. Each sign is indicated on the horizontal axis, and along the vertical axis "most," "middle," and "least" indicate the position occupied by each group in relation to the others. When the same number of persons in two groups evidenced a particular sign, the two groups are indicated at the same position on the graph, the point being an average of the two remaining rankings.

It is apparent from Chart 2 that scores for the myxedematous group generally tend to fall in the middle, that the neurotic group tends to have least signs, and that
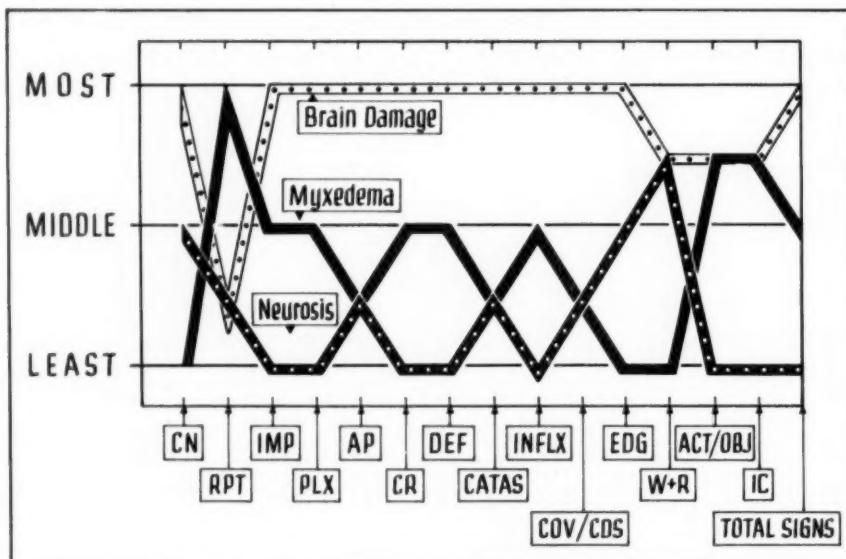
Chart 2.—Comparative rankings of neurotic, myxedematous, and brain-damaged groups with relation to the frequency of occurrence of Rorschach test "signs" of brain damage.

the brain-damaged patients have most. The indication for *Total Signs* bears out this trend.

Table 5 presents chi-square values (computed with Yates's correction for continuity) which compare the numerical frequencies with which the signs occurred in the three groups.

Relatively few of these chi-square values are significant. Two signs (impotence and concrete responses) differentiate the brain-damaged and the neurotic group at the 0.01 level, and two others (perplexity and catastrophic reaction), at the 0.05 level. Only impotence occurs more frequently when the neurotic and the myxedema-

19. Halstead, W. C.: Brain and Intelligence: A Quantitative Study of the Frontal Lobes, Chicago, University of Chicago Press, 1947.

TABLE 5.—*Chi-Square Values Comparing Frequency of Occurrence of Rorschach Test "Signs" of Brain Damage in Three Diagnostic Groups*

Groups	Cn	Rpt	Imp	Pix	AP	CR	Def	Catas	Inflx	CovCds	Edg	W&R	ActObj	IC	Total Signs
Neurosis vs. myxedema	0	0	4.28	2.72	0	1.42	0.14	0	0	0	0	0.24	1.68	0	5.44
Neurosis vs. organic brain damage	0	0	13.60	5.40	0	6.64	2.14	4.04	2.60	2.92	0	0	1.68	0	19.20
Myxedema vs. organic brain damage	1.08	0	2.94	0.53	0	2.14	1.20	4.04	0.58	2.92	1.08	0.24	0	0	11.12

tous group are compared, and that at the 0.05 level. The brain-damaged subjects show catastrophic reactions to the test more frequently than the myxedematous subjects (0.05 level). It would seem, then, that the myxedema group differs from the neurosis group in the direction of the brain-damage group with respect to impotence, or doubting the adequacy of responses with inability either to withdraw or to improve them, and differ from the brain-damage group in the direction of the neurosis group with respect to the expression of emotion arising from frustration with the task (catastrophic reaction). It is worth while to note that comparisons of the total frequency of signs in the three groups are significantly different. The brain-damaged group showed more signs than the other two groups at the 0.01 level, and the myxedematous group, more than the neurotic group at the 0.05 level.

A review of the Rorschach test records was made in an attempt to determine any outstanding features in interpretation common to the three groups. The records of the neurotic subjects showed, as would be expected, definite trends toward anxiety and depression. The records of the brain-damaged subjects, while showing the characteristic "signs" of brain damage, also evidenced considerable anxiety and instances of depression. These personality disturbances associated wth the after-effects of brain damage have been commented on before.[17a] The records for the myxedematous subjects ranged from ones that appeared essentially normal through ones that seemed typically neurotic to records strongly evidencing the characteristic manifestations of severe brain damage. Two of these, while giving evidence of brain damage, also showed many schizophrenia-like characteristics. While these indications may be reliably associated with the duration and severity of changes associated with thyroid deficiency, any attempt to establish the relationship must be omitted from this study. Collaborative research among endocrinologists, psychiatrists, and psychologists may well be necessary to provide sufficiently complete information with regard to the correlation between personality changes and duration and severity of myxedema.

Although the present study presents evidence with regard to measurable mental changes in myxedema, the findings are at best preliminary and relatively nonspecific. Further investigation should be carried out in attempting to answer the question of whether or not the intellectual impairment in myxedema is reversible. A pretreatment and post-treatment design using an equated control group should answer this question. In the present investigation post-treatment measurement was originally anticipated, but facilities were lacking for the enticement of patients back to the laboratory once treatment had liberated their pathological symptoms. Two conditions should be met in attempting to specify further the nature of the mental changes associated with myxedema. First, a larger group should be studied to permit more adequate generalization, and, second, a greater variety of tests should be used.

SUMMARY AND CONCLUSIONS

The Rorschach test was administered to three diagnostic groups: neurotic subjects, myxedematous subjects, and subjects with organic brain damage. The subjects had been individually matched in the three groups on the basis of sex, age, formal education, and intelligence quotients. Intergroup statistical comparisons were made of the mean performances on each of the Rorschach test variables. The frequencies

with which scores in one group exceeded the matched scores in the other groups were tabulated and the frequency differences tested for statistical significance. The frequencies of Rorschach test "signs" of organic brain damage in the three groups were also compared statistically.

The results give a general indication that intellectual functions, as represented by the Rorschach test, suffer some impairment with myxedema. The performance of myxedematous patients falls between that of neurotic patients and that of patients with organic brain damage. In some respects their scores more closely resemble those for neurotic subjects and in others the scores for brain-damaged subjects. The specific nature of the intellectual dysfunction in myxedema was not thoroughly indicated in the present study. A greater number of subjects and a wider variety of psychological tests should be used in seeking more specific results.

SYMPTOMS AND SIGNS REFERABLE TO THE BASAL GANGLIA IN BRAIN TUMOR

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CEREBRAL tumor is not generally considered a cause of extrapyramidal signs and symptoms, and it has been stated by Kinnier Wilson [1] and others [2] that neoplastic involvement of the basal ganglia is often asymptomatic. Focal neurologic signs are not usually observed until the internal capsule is involved. The relevant literature consists largely of individual case reports. It is the purpose of this paper to describe a series of 12 cases of intracranial tumor and manifestations indicating involvement of the extrapyramidal system and to review the pertinent literature.

In 1923 Parker [3] described the case of a 12-year-old boy with a clinical picture of Parkinsonism who was found to have a tumor involving both thalami. Moersch [4] in 1928 reported the case of a man aged 28 with Parkinsonian facies and gait and a tremor of the left upper extremity who recovered completely after the removal of a right parasagittal meningioma.

The patient of Hunt and Lisa [5] was a man aged 29 whose mask-like appearance, tremor, and slow gait appearing in the course of a brief illness with severe headache and lethargy led to the diagnosis of epidemic encephalitis. Spinal fluid studies showed increased globulin and 6 lymphocytes per cubic millimeter. Autopsy revealed a fibrosarcoma arising from the meninges over the right frontal lobe. It was stated that "the basal ganglia on the side of the tumor were compressed to one-half normal size."

Van Bogaert,[6] in an article on infundibular tumors, reported the case of a woman aged 46 with a four-year history of seizures and a one-year history of

1. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940, Vol. 2, p. 1243.

2. Ody, F.: Tumors of the Basal Ganglia, Arch. Neurol. & Psychiat. **27**:249 (Feb.) 1932.

3. Parker, H. L.: Tumors of the Brain Simulating Epidemic Encephalitis and Involving the Third Ventricle, the Fourth Ventricle, and the Basal Ganglia: Report of 3 Cases, J. Nerv. & Ment. Dis. **58**:1 (July) 1923.

4. Moersch, F. P.: Tumors of the Frontal Lobe Presenting a Parkinsonian Syndrome, Minnesota Med. **11**:734 (Nov.) 1928.

5. Hunt, E. L., and Lisa, J. R.: Frontal Lobe Tumor: A Case Simulating Epidemic Encephalitis, with Parkinson's Syndrome, J. A. M. A. **89**:1674 (Nov. 12) 1927.

6. van Bogaert, L.: Thalamic and Parkinsonian Types of Infundibular Tumors: Occurrence of Glycoregulatory and So-Called Endocrine Disorders, Arch. Neurol. & Psychiat. **19**:377 (March) 1928.

diminishing vision who "moved in one piece" and exhibited retropulsion, slowness of movement, and diminished mimicry. He related this instance of "true Parkinsonism" to pressure on the basal ganglia from a basal tumor.

The existence of generalized Parkinsonism in connection with unilateral tumor was considered noteworthy by Stern,[7] whose patient was a woman aged 38 with a five-year history of progressive rigidity, reduced facial mobility, and tremor. The calcified outline of an extensive tumor in the depths of the right hemisphere was seen in roentgenograms of the skull.

In 1943 Grant[8] collected from the literature 16 cases of brain tumor with Parkinsonian manifestations and added 1 case. His patient was a man aged 26 with a two-year history of widespread paresthesias, followed by hallucinations of sight, smell, and hearing. There was a constant tremor of the right foot. Autopsy revealed hippocampal herniation due to a large astrocytoma arising from the medial centrum of the left temporal lobe. There was considerable edema in the neighborhood of the neoplasm, and the left lenticular nucleus and the basilar portion of the adjacent cerebral peduncle were compressed.

Urechia, Dragomir, and Usinievici[9] reported the case of a boy aged 14 whose illness began with progressive spastic contracture of the hand, followed by torsion spasm of that side of the body. Two years later, at autopsy, he was found to have a glioblastoma in the contralateral hemisphere compressing and destroying the putamen, caudate nucleus, and part of the globus pallidus. In 1947 Mettler, Davidoff, and Grimes[10] described a patient who exhibited an alternating tremor at rest of the right upper and lower extremities at the age of 6 years. She was treated with x-rays for an inoperable tumor of the floor of the third ventricle. During the ensuing seven years right hemiplegia developed. The right upper extremity was flexed and always in motion while the patient was awake. At autopsy a massive polar spongioblastoma was found to involve the diencephalon and mesencephalon, with compression and infiltration of the left thalamus, as well as the midbrain.

Ody,[2] in 1932, studied a series of 25 tumors involving the basal ganglia and came to the conclusion that there were no specific signs referable to neoplastic invasion of these structures. Schlesinger[11] reported a 35% incidence of signs referable to the basal ganglia in a series of 20 patients with gliomas involving primarily the splenium of the corpus callosum.

During the past two years, 474 patients with brain tumor were admitted to the Neurological Institute of New York. At least 10 of these patients, about 2%, manifested extrapyramidal symptoms and signs and are included in this report. Two additional patients (Cases 1 and 2) were seen several years previously.

7. Stern, A.: Parkinsonism Due to a Cerebral Tumor, Harefuah 30:138, 1936.

8. Grant, W. T.: Brain Tumor with Parkinsonian Manifestations: Report of a Case, Bull. Los Angeles Neurol. Soc. 8:139 (Dec.) 1943.

9. Urechia, C. I.: Dragomir, L., and Usinievici, G.: Spasme de torsion unilatéral causé par une tumeur cérébrale, Confinia neurol. 5·271, 1943.

10. Mettler, F. A.; Davidoff, L. M., and Grimes, R.: Static Tremor with Hemiplegia: Report of a Case; Development, Progression for 7 Years and Postmortem Histologic Observations, Arch. Neurol. & Psychiat. 57:423 (April) 1947.

11. Schlesinger, B.: Gliomas Involving the Splenium of the Corpus Callosum, Neurology 1:419 (Nov.-Dec.) 1951.

REPORT OF CASES

CASE 1.—*Generalized convulsions for six years and tremor of left hand for several weeks; masked facies, slow gait, tremor, and retropulsion. Astrocytoma deep in right frontal lobe encountered at operation.*

H. A., a man aged 39, was admitted to the hospital on Dec. 22, 1936, with a six-year history of convulsions and a three-year history of personality change. During the few weeks preceding admission a rhythmical tremor of his left hand was noticed. On examination there were observed masking of the facies, slowness of gait, and retropulsion. The left arm swing was diminished, and there were intermittent rhythmical movements of the outstretched fingers of the left hand. Facial weakness and hyperreflexia were noted on the left side, but the plantar responses were normal. There was no papilledema. The roentgenograms showed that the pineal gland was displaced upward. The Parkinsonian features noted on examination and the freedom from signs of increased intracranial pressure cast doubt on the presumptive diagnosis of cerebral neoplasm. However, a pneumoencephalogram revealed that the lateral and third ventricles were displaced to the left. The roentgenologist's diagnosis was tumor of right frontal lobe located at the point of the Sylvian fissure. The cerebrospinal fluid removed at the time of air injection contained 16 mg. of protein per 100 cc. and no cells. Permission for operation was refused, and the patient left the hospital, only to be readmitted on March 24, 1937, because of severe headache and increasing frequency of seizures. The tremor had become worse. Reexamination showed an intermittent tremor of the left upper extremity, hyperreflexia on the left side, and bilateral extensor plantar responses. A right frontotemporal craniotomy was performed, and tumor tissue was encountered 3 cm. below the cortex of the right frontal lobe and extending down to the island of Reil. The biopsy diagnosis was astrocytoma. Death occurred on the second postoperative day, and permission for autopsy was not obtained.

CASE 2.—*Tremor of left upper extremity for two months, followed by rhythmical tremor of the other extremities. Astrocytoma beneath splenium of corpus callosum, extending into both thalamic areas.*

F. E., a man aged 32, was admitted to the hospital on March 18, 1942. Ten months prior to admission he began to have attacks of unconsciousness. A month later he noted headache. For two months he was aware of a tremor of the left upper extremity. On examination he was observed to be confused and to walk with a slow gait. There was loss of associated arm movements. He presented a mask-like facies, bilateral papilledema, left facial weakness, slurred speech, and hypesthesia of the left side. A coarse, rhythmical tremor at rest involved all extremities, especially the left upper extremity, where cogwheel rigidity was also present. There was evidence in the x-ray films of generalized increased intracranial pressure. Electroencephalograms revealed a large deep focus of abnormal activity, which was more prominent over the right side. The diagnosis of a deep tumor of the third ventricle, probably arising from the wall of the ventricle, was made by ventriculography. Operation, performed on the fifth hospital day, revealed a large tumor beneath the splenium of the corpus callosum. Death occurred on the second postoperative day. The biopsy diagnosis was astrocytoma. Permission for autopsy could not be secured.

CASE 3.—*Tremor of left arm and foot for nine years. Tumor of right thalamus found at autopsy.*

E. T., a woman aged 21, a college student, was admitted to the hospital on Jan. 7, 1952. Nine years prior to admission she first noted a slight tremor of the left upper extremity. Within a year the tremor had involved the left foot also. Four years before hospitalization she began to experience occasional fainting spells. For one year prior to admission there were paresthesias of the left side of the body. She had been observed regularly for several years by a neurologist, who had described the abnormal movements as athetoid. On examination the patient was noted to be lethargic. There was slight blurring of the margins of both optic disks. Mild weakness and an extensor plantar response were noted on the left side. Irregular movements of the left hand, which ranged from an alternating tremor to athetotic movements of wider amplitude, were present. This motion was present in the left foot to a less severe degree. The cerebrospinal fluid was xanthochromic, with an initial pressure of 280 mm. of water, 350 mg. of protein per 100 cc., and 4 lymphocytes per cubic millimeter. The electroencephalogram was diffusely abnormal. Enlargement of the blind spots was observed on examination of the visual fields. Dilatation of

both lateral ventricles and elevation of the body of the right lateral ventricle were demonstrated by pneumoencephalography. The roentgenologist's diagnosis was tumor in the region of the right thalamus (Fig. 1). The patient's condition became progressively worse, and at operation a tumor was seen in the right thalamic region. She died four days later. Autopsy revealed that the tumor had invaded the thalamus, lenticular nucleus, and island of Reil on the right side (Fig. 2). It had also extended into the cisterna ambiens and compressed the midbrain from the right. The tumor was a mixed oligodendroglioma and astrocytoma which had undergone glioblastomatous degeneration.

CASE 4.—*Intermittent tremor of right upper extremity for three weeks and generalized slowing of all motor activity; mask-like facies and shuffling gait. Glioblastoma of the left frontal region.*

M. K., a man aged 65, a garment worker, was admitted to the hospital on July 24, 1951, with a three-week history of intermittent tremor of the right upper extremity, slowness and unsteadiness in walking, and generalized retardation of all motor activity, including speech. During the previous three months he had shown a lack of spontaneity and had become apathetic.

Fig. 1 (Case 3).—Pneumoencephalogram. The floor of the body of the lateral ventricle was elevated by the tumor in the right thalamus.

He was obtunded and disoriented, exhibiting little spontaneous speech and considerable poverty of movement. He walked with a slow, shuffling gait. Associated movements of the upper extremities were restricted. There were cogwheel rigidity of the right arm and an intermittent spontaneous tremor of both upper extremities, more pronounced on the right. The facies was mask-like. The reflexes were normal. There was bilateral papilledema, and retinal hemorrhages radiated from the margins of both optic disks. In the x-ray films the pineal gland appeared shifted 5 mm. to the right and displaced posteriorly. The electroencephalogram showed a focus of abnormal activity in the left temporoparietal area. Ventriculograms were interpreted as indicating the presence of a large, deeply situated tumor of the left frontal lobe. A left frontal craniotomy was done, with uncapping of a large cyst and removal of its semisolid contents. The pathological diagnosis was glioblastoma. The patient was discharged, to receive radiation therapy at another hospital, nearer his home. He died on Feb. 18, 1952. Permission for autopsy was not obtained.

CASE 5.—*Left oculomotor nerve paralysis for 20 years; choreoathetotic movements of right upper extremity for 3 years. Fibroma of left choroidal fissure, compressing basal ganglia and cerebral peduncle on left side.*

J. M., a housewife aged 29, was admitted to the hospital for the third time on Jan. 24, 1951. She had been followed irregularly over a 20-year period because of a persistent left oculomotor nerve paralysis. In 1937 she began to experience involuntary jerking movements of the right hand and arm. When she was admitted to the hospital, two years later, there were gross, irregular choreoathetoid movements of the right upper extremity. The reflexes and sensory status were normal. The cerebrospinal fluid pressure was 285 mm. of water, and the protein content was 161 mg. per 100 cc. Roentgenograms disclosed small areas of calcification above and to the left of the posterior clinoid processes. Opinion was divided between the diagnostic possibilities of craniopharyngioma and aneurysm of the left internal carotid artery. When she was examined in 1940, abnormal movements were not noted. The spinal fluid protein had increased to 396 mg. per 100 cc. For six months prior to her last admission she had been having frequent attacks of loss of consciousness. The day prior to admission she had two such attacks. She fell to the floor during the second episode and lapsed into coma. Upon arrival at the hospital she was moribund and exhibited a decerebrate type of rigidity. There were bilateral extensor
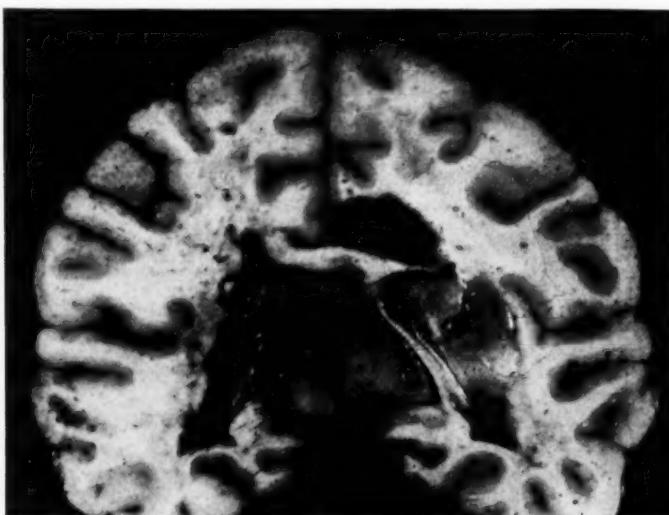
Fig. 2 (Case 3).—Coronal section at the level of the atria, through the posterior portion of the thalamic tumor. Part of the operative tract is seen in the region of the right cingulate gyrus.

plantar responses, right hyperreflexia, and right oculomotor nerve paralysis. She died 13 hours after admission. At autopsy a large firm encapsulated tumor was found at the base of the brain. This nested in the left choroidal fissure and compressed the lenticular nucleus, hypothalamus, cerebral peduncle, midbrain, and rostral portion of the pons on the left side (Fig. 3). The terminal coma was the result of a fracture of the left temporal bone, with laceration of the left middle meningeal artery and a huge epidural hemorrhage on the left side. The tumor was a fibroma, containing areas of calcification.

CASE 6.—*Rhythmical tremor of right upper and lower extremities of several days' duration. Glioblastoma multiforme of left frontotemporal area.*

L. P., a man aged 65, was admitted to the hospital on April 10, 1952. During the two weeks preceding admission it was noted that he had become depressed, lethargic, and reluctant to speak. The difficulty with speech progressed. He stroked his head frequently and acted as if he was in pain. Several days before hospitalization his right hand began to shake. Examination showed that he was unable to stand and was aphasic. The margins of both optic disks were blurred.

There were slight weakness of the right hand and minimal preponderance of the deep reflexes on the right. A rapid rhythmical alternating tremor of the right upper extremity was apparent. During the subsequent 24 hours this tremor became more pronounced and extended to involve the right lower extremity. There was some rigidity of the right upper extremity. Roentgenograms of the skull revealed nothing significant. The pineal gland was not visualized. An electroencephalogram was diffusely abnormal. A deeply situated mass was demonstrated in the left frontotemporal region by ventriculography. An operation was performed on the second hospital day. A large, widely infiltrating, necrotic tumor was found involving the left frontal and temporal lobes, the thalamus, and the basal ganglia. The patient died on the following day. The biopsy diagnosis was glioblastoma multiforme. Permission for an autopsy could not be obtained.

CASE 7.—*Progressive contracture of left hand for one month and involuntary movements of left great toe for two weeks. Glioblastoma of right frontal lobe, involving basal ganglia and thalamus.*

M. K., a school girl aged 15, was admitted to the hospital on Oct. 23, 1951, complaining of spasm of the fingers of the left hand for one month and jerking movements of the left great toe for two weeks. She had subsequently lost the ability to extend the fingers of her left hand.

Fig. 3 (Case 5).—Fibroma nesting in the left choroidal fissure and compressing the basal ganglia on that side. Flattening of the convexity of the left hemisphere was caused by the epidural hemorrhage.

Her family reported that her face had appeared asymmetrical for several weeks. The left thumb showed rigid hyperextension, whereas the other fingers of that hand were flexed at the metacarpophalangeal and proximal interphalangeal joints but were extended at the distal interphalangeal joints. There was depression of associated movements of the left upper extremity. This arm was at times held rigidly in pronounced internal rotation and adduction at the shoulder, with the hand behind the body, or flexed at the elbow and adducted at the shoulder. There was occasional slow involuntary and irregular dorsiflexion of the left great toe, associated with plantar flexion of the smaller toes and an inverted position of the left foot. The tonus of the left upper extremity was generally increased. There were moderate weakness of the left side, more pronounced in the upper extremity, and weakness of the left side of the face. The deep reflexes were normal. The left plantar response was difficult to evaluate, since the left great toe was usually in a position of dorsiflexion. The cerebrospinal fluid was under an initial pressure of 150 mm. of water and contained 2 lymphocytes per cubic millimeter and 78 mg. of protein per 100 cc. A group of calcium shadows deep in the right parasagittal area were seen in the x-ray films (Fig. 4A). The pineal was not calcified. The roentgenologist considered these changes to

be the result of calcific degeneration in a glioma of the thalamic area. A deep-seated mass which involved the region of the thalamus and basal ganglia was found on ventriculography (Fig. 4B). A right frontal craniotomy was performed, and grayish-purple cystic tumor tissue was removed down to the level of the right lateral ventricle. After operation, all abnormal movements disappeared, and there were flaccid left hemiplegia and left homonymous hemianopsia. Radiation therapy was of no benefit, and the patient died three months after the operation. At autopsy the neoplasm was found to have extended throughout the right frontal lobe, basal ganglia, right thalamus, and right side of the corpus callosum (Fig. 5). Microscopically, nearly all portions of the neoplasm showed a high order of malignancy, and the histologic diagnosis was glioblastoma.

CASE 8.—*Rhythmical tremor of both hands for two weeks. Large infiltrating glioblastoma multiforme of the corpus callosum, extending into the right thalamic region.*

R. K., a man aged 63, was admitted to the hospital on March 29, 1951, with a two-week history of memory loss, headache, and tremor of both hands. He was disoriented. There were minimal papilledema and, on the left side, facial weakness, hypesthesia, and mild weakness of the upper extremity. The deep reflexes were hyperactive on that side. His gait was slow and hesitant. A rhythmical alternating tremor, at a rate of 3 to 5 per second, was present in both hands. There was cogwheel rigidity of both upper extremities. X-ray examination of the skull
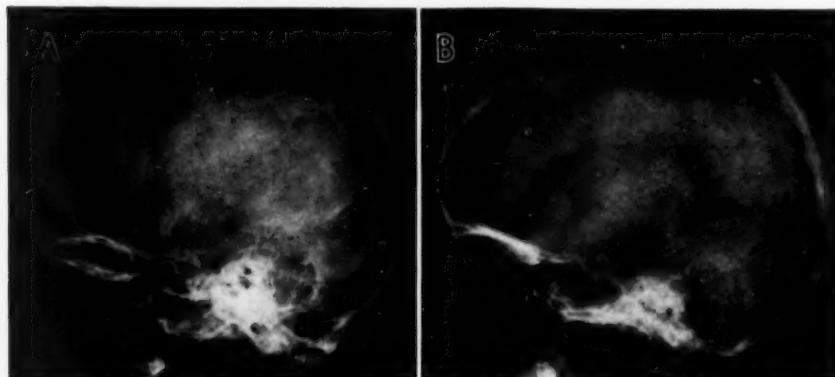
Fig. 4 (Case 4).—*A*, pathologic calcium shadows, which are the result of calcific degeneration in the tumor. *B*, ventriculogram; the body of the right lateral ventricle is shown to be largely occluded by the deep-seated cerebral tumor on that side.

showed nothing significant. The electroencephalogram was mildly abnormal. A deep parietal mass was revealed by ventriculography. An operation was performed on the fourth hospital day, and tumor tissue was found in the posterior parietal region. The patient died four days later. Autopsy revealed a large infiltrating glioblastoma multiforme arising in the splenium and the body of the corpus callosum (Fig. 6). It invaded the right thalamic region and the white matter of the temporal and parietal lobes.

CASE 9.—*Rhythmical tremor of right hand of five weeks' duration. Metastatic carcinoma in right parieto-occipital area.*

W. A., a man aged 58, was admitted to the hospital on March 22, 1951. He had first noted the onset of headache and tremor of the right hand about five weeks before admission. Gait was unsteady. There were bilateral papilledema, mild right facial weakness, horizontal nystagmus, and a rhythmical 3-to-5-per-second tremor of the right upper extremity at rest. An area of increased density at the apex of the right lung was considered by the roentgenologist as evidence of an old inflammatory lesion. X-ray films of the skull disclosed a 5-mm. shift of the pineal body to the left and evidence of generalized increased intracranial pressure. Ventriculograms revealed depression of the roof of the right lateral ventricle, indicating a right parietal tumor. At operation partial removal of a right parieto-occipital tumor was accomplished. The patholo-

gist's diagnosis was metastatic carcinoma, primary site unknown. Left hemiplegia developed after the operation. On April 14, 1951, the patient was transferred to another hospital for chronic care.

CASE 10.—*Blindness of right eye for seven years; seizures for four years; rhythmical tremor involving first the left and then the right upper extremity. Roentgenographic diagnosis of meningioma of right sphenoidal ridge.*

A. S., a man aged 57, was admitted to the hospital on April 12, 1951, with a seven-year history of blindness of the right eye and a four-year history of seizures. He had one to four atacks each month consisting of brief lapses in consciousness, during which he stared into space, breathed heavily, and occasionally moved his upper extremities and shuffled his feet. There were mild postictal confusion and amnesia. During the year preceding admission he noticed shaking of his left hand and, later, a similar tremor of the right hand. There were slowing of all movements and stiffness in walking. On examination he appeared as a stooped, elderly white man, who walked slowly and moved *en bloc*. The left-arm swing was diminished.
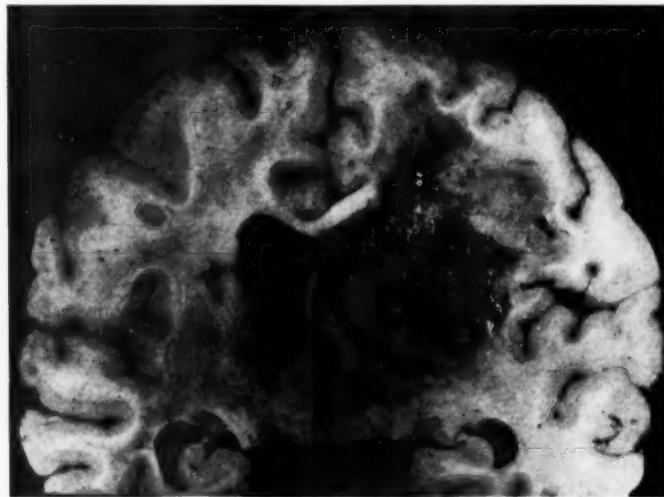
Fig. 5 (Case 7).—Glioblastoma multiforme involving the right basal ganglia, thalamus, and central white matter.

There was cogwheel rigidity in all extremities. A bilateral rhythmical alternating 3-to-4-per-second tremor was present in both upper extremities, and there was a pill-rolling movement of each hand. The deep reflexes were hyperactive on the right, and there was an extensor plantar response on that side. The right optic disk was pale. The right eye was blind, and corrected visual acuity in the left eye was 20/100, with a normal field of vision. The cerebrospinal fluid pressure was 190 mm. of water, with 2 lymphocytes per cubic millimeter and 133 mg. protein per 100 cc. of cerebrospinal fluid. The electroencephalogram was diffusely abnormal, with a highly suggestive focus in the right parietotemporal area. On x-ray examination, the pineal was found to be shifted 5 mm. to the left, and the right sphenoidal ridge was greatly thickened. Just above this dense ridge were irregular shadows of calcium density. The roentgenologist's diagnosis was meningioma of the right sphenoidal ridge. In view of the far-advanced hypertensive cardiovascular disease, the patient was not considered a suitable candidate for operation.

CASE 11.—*Bradykinesia, masked facies, and rhythmical tremor of the left extremities. Deep-seated tumor in right frontal area. Disappearance of tremor and rigidity after subtemporal decompression.*

S. A., a man aged 45, was admitted to the hospital on Feb. 21, 1952, with a 2-week history of generalized headache and a 10-day history of unsteadiness of gait. There was one episode of olfactory hallucination five days prior to admission, when he smelled the odor of burning food. On examination, his movements and responses were noted to be slow, and he exhibited masking of facial expression. There was increased muscle tonus on the left, and the cogwheel phenomenon could be demonstrated in the left upper extremity. An intermittent rhythmical tremor of the left extremities was noted. On the left side there were slight weakness, hyperreflexia with an extensor plantar response, and facial weakness. X-ray examination of the skull revealed nothing of significance. A ventriculogram showed evidence of a tumor deeply situated in the right frontal area. A right frontotemporal craniotomy was done, and a transcortical incision was carried down to a depth of 5 cm., where yellow tissue was encountered; but the tumor was not exposed. A subtemporal decompression was done, and the patient was treated with x-radiation. He showed moderate improvement at the time of discharge, when he walked well and no longer exhibited the tremor or rigidity.

CASE 12.—*Tremor and athetosis of right arm of two months' duration. Mass in left thalamic region demonstrated by pneumoencephalography.*
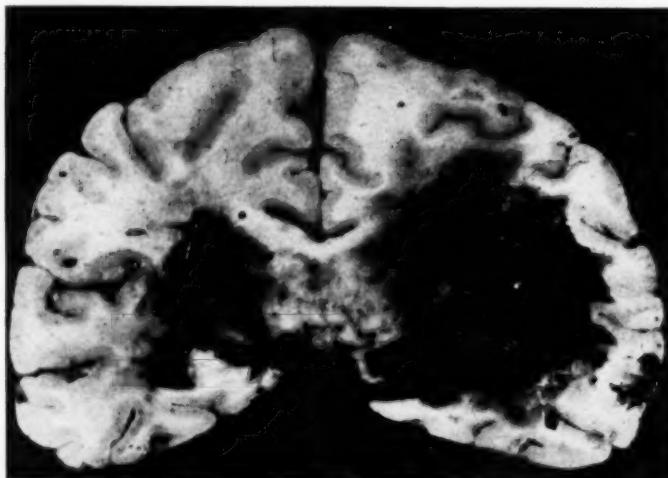
Fig. 6 (Case 8).—Glioblastoma multiforme in the posterior portion of the body and splenium of the corpus callosum and extending bilaterally into the central white matter. The hemorrhage arose in the operative area and extended into the ventricles.

E. D., a housewife aged 40, was admitted to the hospital on Nov. 26, 1951, complaining of involuntary movements of the right hand of two months' duration. For a month she had noted headaches and some loss of memory. Examination revealed slow, writing, athetotic movements of the fingers and wrist of the right hand, and occasionally a slow alternating rhythmical tremor of the fingers of the same hand. The other pertinent findings included facial weakness and mild hemiparesis on the same side. During the subsequent month of hospitalization, the movements became more pronounced and spread to involve the entire right upper extremity. The right hemiparesis then progressed to hemiplegia, and the abnormal movements disappeared. Global aphasia also developed. Cerebrospinal fluid, obtained at the time of pneumoencephalographic study, contained 29 mg. of protein per 100 cc. and 1 lymphocyte per cubic millimeter. The Kolmer reaction was negative, and the colloidal gold curve was normal. X-ray films disclosed that the pineal gland was shifted 3 to 5 mm. to the right and was displaced posteriorly. The electroencephalogram showed low-voltage rapid activity in both frontal areas. Evidence of a tumor deep to the posterior portion of the left lateral ventricle in the left thalamic area was found by pneumoencephalography. X-ray therapy was of no benefit. She was discharged to another hospital for chronic care three months after admission.

COMMENT

These 12 cases represent a histologically varied group of tumors, which includes five glioblastomas, two astrocytomas, one fibroma, one metastatic carcinoma, and three unverified tumors. One of the last-mentioned tumors (Case 10) was in all probability a meningioma of the sphenoidal ridge.

Symptoms.—Eleven of the 12 patients had the presenting complaint of abnormal involuntary movements. The duration of this symptom prior to admission ranged from several days to nine years. In addition to the tremor, the patients had other signs and symptoms of damage to the basal ganglia (described in detail below) and some of the symptoms commonly associated with an expanding intracranial lesion. Eight patients complained of headache; six were said to exhibit

Summary of Signs of Basal Ganglia Involvement

Case No.	Age. Yr.	Sex	Extrapyramidal Manifestations						Other Signs	Diagnosis
			Tremor	Athetosis	Rigidity	Decreased Associated Movements	Slowness	Masked Facies		
1	39	M	+	—	—	—	+	+	Blepharo-spasm; retro-pulsion	Astrocytoma (craniotomy)
2	32	M	+	—	+	+	+	+	—	Astrocytoma (craniotomy)
3	21	F	+	—	+	+	—	—	Posturing of hand	Mixed glioma with glioblastomatous change (autopsy)
4	65	M	+	—	+	+	+	+	—	Glioblastoma (craniotomy)
5	29	F	—	+	—	+	—	—	—	Fibroma (autopsy)
6	65	M	+	—	+	—	—	—	—	Glioblastoma (craniotomy)
7	15	F	—	+	+	+	—	—	Posturing of arm	Glioblastoma (autopsy)
8	63	M	+	—	+	—	+	—	—	Glioblastoma (autopsy)
9	58	M	+	—	—	—	—	—	—	Metastatic carcinoma (craniotomy)
10	57	M	+	—	+	+	+	—	—	Sphenoid ridge meningioma (x-ray)
11	45	M	+	—	+	—	+	+	—	Mass deep in right frontal area (ventriculogram)
12	40	F	+	+	—	—	—	—	—	Mass in left thalamus (pneumoencephalogram)

personality change, and five had seizures. One patient complained of nausea and vomiting, and another had olfactory hallucinations.

Signs and Laboratory Data.—Seven patients had evidence of pyramidal tract involvement, and three of these also had facial weakness. Facial weakness without concomitant pyramidal tract signs was present in an additional three patients. Frank papilledema was present in four patients. Hypesthesia of one-half the body was noted in two patients. Two patients had aphasia.

The spinal fluid pressure was measured in four cases, in two of which it was elevated. The spinal fluid protein was increased in four of the six cases in which it was estimated. A shift of the pineal body was seen in 5 of the 12 routine x-ray studies of the skull; abnormal calcification was present in 3, and roentgenographic signs of increased intracranial pressure were detected in 2. An electroencephalographic focus was reported in four cases.

The following signs of basal ganglia involvement were observed (Table).

Tremor.—In 10 cases tremor of one or more extremities was exhibited, in 8 of which it was described as rhythmical and alternating. In four of the latter cases the frequency of the tremor was recorded as 3 to 5 per second. This type of tremor is not to be confused with the tremor observed by Stewart.[12] In 18 of his 20 cases of frontal lobe tumor there was a fine rapid tremulous movement of the extended upper limb on the same side as the growth. The ages of our patients who exhibited tremor ranged from 21 to 65; five of them were over 45. In the patients in the older age group the possibility of brain tumor coexisting with Parkinson's disease must be considered.

In Case 4, that of a man aged 65, the tremor had been present for only six weeks and on examination was found to involve both hands, especially the right, with cogwheel rigidity of the right arm. In Case 6, that of a man aged 65, the tremor of the right hand had been present for only several days and was contralateral to the tumor. In Case 8, that of a man aged 63, there was a two-month history of progressive tremor of both hands and, on examination, a rhythmical alternating 3-to-5-per-second tremor at rest. There was cogwheel rigidity in both upper extremities. In Case 9, that of a man aged 58, there was a five-week history of tremor of the right hand. He was the only patient in this group whose tremor was present on the same side as the tumor, and since he was found to have a metastatic tumor, it is possible that multiple cerebral lesions were present. In Case 10, a man aged 57, with a presumptive diagnosis of meningioma of the right sphenoidal ridge, had complained of a tremor of the left hand for one year but on examination was found to have also a slight tremor of the right hand.

Thus, in four of these five patients in the older age group, the tremor was of very brief duration. In three patients the tremor was contralateral to the tumor, and in one it was bilateral. With the possible exception of the last patient (Case 10) in whom the coexistence of Parkinson's disease cannot categorically be denied, it is likely that the tremor was a manifestation of the tumor in these older patients.

Athetosis.—Instances of choreoathetosis associated with cerebral tumor were reported by Hyndman and Van Epps [13] and by Roback and Waraich.[14] Four patients in the present series exhibited athetotic or choreoathetotic movements. One of them, a 15-year-old girl (Case 2), also exhibited a torsion spasm of the left hand and posturing of the left upper extremity. Posturing was also present in the third patient.

Rigidity.—Seven patients were found to have rigidity, and five of these also presented cogwheel rigidity of the muscles.

Other Manifestations.—Poverty of movement (six patients), masked facies (four patients), decreased associated movements (six patients), retropulsion (one patient) and blepharospasm (one patient) constitute the remaining extrapyramidal signs of note in this series of patients.

12. Stewart, T. G.: A Note upon 2 Important Points in the Localization of Tumors of the Frontal Region of the Brain, Rev. Neurol. & Psychiat. 4:809 (Dec.) 1906.

13. Hyndman, O. R., and Van Epps, C.: Tumor of the Thalamus: A Ventriculographic Entity, Arch. Surg. 39:792 (Nov.) 1939.

14. Roback, H. N., and Waraich, G. S.: Tumor of the Thalamus and Calcaroid Deposits in Globus Pallidus, Bull. Menninger Clin. 1:285 (Nov.) 1937.

The cases of Parker [3] and of Lisa and Hunt,[5] previously cited, were at first considered to be instances of encephalitis. Prior to pneumoencephalographic study one of our patients (Case 1), who exhibited blepharospasm, retropulsion, masked facies, and tremor, was thought by some examiners to have postencephalitic Parkinsonism.

That unilateral cerebral neoplasms may be associated with generalized Parkinsonism was indicated by Moersch [4] and Stern.[7] Four of the present series (Cases 1, 4, 7, and 10) fell into the same category.

SUMMARY

A series of 12 cases of cerebral tumor and extrapyramidal manifestations is reported.

A rhythmical, alternating tremor was the commonest extrapyramidal symptom in this group of cases.

Other extrapyramidal manifestations included athetosis, torsion spasm, posturing, rigidity, and bradykinesia.

A differential diagnosis of Parkinson's disease and Parkinsonism with brain tumor must be made in a small percentage of cases. Consideration of (1) the age of the patient, (2) duration and location of extrapyramidal signs, and (3) other neurological signs and symptoms may facilitate this differentiation. However, more definitive diagnostic tests, such as pneumoencephalography or ventriculography, may be necessary.

ENDOGENOUS EOSINOPENIA IN INSTITUTIONALIZED PATIENTS WITH MENTAL DEFICIENCY

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A TWENTY-four-hour rhythm in circulating eosinophiles has been established for certain mammals.[1] A decrease in numbers of eosinophiles from 6:30 to 9:30 of the same morning is usually characteristic of this rhythm in mature, healthy humans habitually arising about 7 a. m. This decrease (in the absence of artificial stimulation other than the subject's daily routine) is designated as endogenous eosinopenia.

The presence of a functioning adrenal cortex seems to be necessary for the manifestation of endogenous eosinopenia. It has been reported that patients with panhypopituitarism and Addison's disease fail to exhibit endogenous eosinopenia,[2] and it is therefore reasonable to infer that an endogenous-eosinopenia test may serve for clinical evaluation of adrenocortical function. If a decrease in numbers of eosinophiles during the morning hours, subsequent to the initiation of activities after awakening, is accepted as reliable evidence of output of eosinopenic corticoids, it would constitute evidence against the diagnosis of panhypopituitarism and/or adrenocortical insufficiency.[3]

1. (a) Halberg, F., and Visscher, M. B.: Regular Diurnal Physiological Variation in Eosinophil Levels in 5 Stocks of Mice, Proc. Soc. Exper. Biol. & Med. **75**:846 (Dec.) 1950. (b) Halberg, F., in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, p. 84. (c) Halberg, F.; Visscher, M. B.; Flink, E. B.; Berge, K., and Bock, F.: Diurnal Rhythmic Changes in Blood Eosinophil Levels in Health and in Certain Diseases, Journal-Lancet **71**:312 (Aug.) 1951.

2. Halberg and Visscher.[1a] Halberg, F.; Flink, E. B., and Visscher, M. B.: Alteration in Diurnal Rhythm in Circulating Eosinophil Level in Adrenal Insufficiency, Am. J. Physiol. **167**:791 (Dec.) 1951.

3. Halberg, F.; Cohen, S. L., and Flink, E. B.: Two New Tools for Diagnosis of Adrenal Dysfunction, J. Lab. & Clin. Med. **38**:817 (Nov.) 1951.

Data on endogenous eosinopenia in patients institutionalized with mental deficiency are presented in this report. Certain procedural implications of these data, arising from recognition of some of the sources of variation in eosinophile levels, will be discussed.

The observation of a morning decrease in numbers of eosinophiles in the population investigated establishes the occurrence of endogenous eosinopenia in mentally deficient patients and thus supports the hypothesis of a functioning adrenal cortex in them. The finding is at variance with an assumption of pituitary-adrenocortical dysfunction in certain patients with mental deficiency.[4] It appears to be of additional interest that these patients had lived for many years in standardized circum-

TABLE 1.—*Clinical Data on Patients Used in the Investigation*

Patient No.	Period of Committ- ment, Yr.	Chrono- logical Age, Yr.	Weight, Lb.	Height, In.	I. Q.
Group 1: Men					
1	17	31	217	71	16
2	21	33	137	67	18
3	23	33	184	68	30
4	23	33	169	68	30
5	34	36	200	65	32
6	17	29	147	71	33
7	19	31	164	62	38
8	18	35	128	63	68
Group 2: Women					
1	40	48	111	61	30
2	21	51	114	64	38
3	14	25	132	63	44
4	14	25	116	61	46
5	19	40	130	64	46
6	14	31	142	60	53
7	27	36	117	56	56
8	23	47	130	62	57
9	14	52	152	61	57
10	14	24	126	61	58
11	14	29	152	63	67
12	23	38	108	60	68

stances of sleep and wakefulness. The time of initiation of their daily activities differed from that of normal subjects studied previously.[1c] Correspondingly, the timing of endogenous eosinopenia in these institutionalized subjects is found to differ from that of normal subjects or of patients [3] who have not experienced similar standardized institutional care over considerable periods of time.

PRESENT INVESTIGATION

Description of Patients.—The subjects of this investigation are identified in Table 1. All belonged to the white race. The 6 men and 12 women comprising the two groups were picked

4. Benda, C. E.: Mongolism and Cretinism: A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency, New York, Grune & Stratton, Inc., 1946.

from the population committed to the institution with the diagnosis of mental deficiency. All were able to walk and talk; some of them were able to do physical work. The range of chronological age at this time was from 29 to 36 years for the men and from 24 to 52 years for the women. Intelligence quotients, listed in Table 1, are the results of applying the Kuhlmann-Binet and Stanford-Binet tests at or shortly after commitment to institutional care.[5] During the 14 to 40 years which the subjects had spent at the institution under observation by physicians and teachers, they had not shown any signs of improvement in mental state. All subjects were

TABLE 2.—*Caloric Content of Diet Available to Both Groups Studied*

Meal	Calories	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast.	560	14	22	77
Dinner.	878	30	50	77
Supper.	718	37	22	93
Total.	2,156	81	94	247

TABLE 3.—*Absolute Eosinophile Counts, Their Daily Mean, and Relative Eosinophile Levels in Group 1 (Men)*

Patient No.	Date[a]	Absolute Eosinophile Count [†]					Relative Eosinophile Level [‡]			
		5	6:30	8	9:30	Mean	5	6:30	8	9:30
1.	a	303	331	212	259	276	110	120	77	94
	b	347	228	300	187	266	131	86	113	70
	c	366	266	366	388	347	106	77	106	112
2.	a	116	69	56	56	74	156	93	75	75
	b	141	81	56	34	78	181	104	72	44
	c	78	75	44	16	53	146	141	83	30
3.	a	194	181	97	137	152	127	119	64	90
	b	212	237	109	103	165	128	143	66	62
	c	248	166	156	119	172	144	96	91	69
4.	a	215	212	131	125	171	126	124	77	73
	b	294	250	203	169	229	128	109	89	74
	c	247	150	206	138	185	133	81	111	74
5.	a	234	178	178	247	209	112	85	85	118
	b	281	200	253	294	257	109	78	98	114
	c	425	303	244	303	319	133	95	77	95
6.	a	450	437	334	453	419	108	104	80	108
	b	316	331	306	222	294	108	113	104	76
	c	1,478	947	1,091	738	1,064	139	89	103	69
7.	a	156	162	119	116	138	113	117	86	84
	b	250	184	81	66	145	172	127	56	45
	c	256	200	163	138	189	135	106	86	73
8.	a	187	219	159	206	193	97	114	82	107
	b	234	253	169	112	192	122	132	88	58
	c	772	584	600	591	637	121	92	94	93

[a] a indicates March 27; b, March 29; c, May 15, 1951.
[†] All counts and levels are for morning hours.
[‡] Count as per cent of daily mean.

retested several times, and it is noted that the maximum intelligence quotient of 68, appearing in Table 1, was never exceeded for any of them in any retest. A diagnosis of mental deficiency for all subjects of this investigation is clearly indicated, not only by these test results but also by past histories and clinical evaluations of the patients. Physical examination one week prior to the investigation failed to reveal clinical or laboratory signs of acute illness. Electroencephalographic records obtained at this time on all subjects were interpreted as normal.

5. Wechsler, D.: The Measurement of Adult Intelligence, Ed. 3, Baltimore, Williams & Wilkins Company, 1944.

Procedures.—At least 24 hours prior to the start of the investigation, the patients constituting each group were transferred from their respective dormitories to a room comparable in size and furnishings. This room was kept at a temperature of $22 \pm 1C$.

The lights were turned off at 9:30 p. m. and on at 6 a. m., when the patients were awakened by a bell. They had been used to getting up at this time since admission to the institution. They ate at 7:30 a. m., at 12 n., and at 5 p. m. The caloric content of the diet, shown in Table 2, was approximately the same on all days of sampling, as well as during the period of equilibration prior to the study. An attendant shared the room with the patients and noted that most of them ate all the food offered.

TABLE 4.—*Absolute Eosinophile Counts, Their Daily Mean, and Relative Eosinophile Levels in Group 2 (Women)*

Patient No.	Date *	Absolute Eosinophile Count †					Relative Eosinophile Level ‡			
		5	6:30	8	9:30	Mean	5	6:30	8	9:30
1	a	137	106	59	53	89	154	119	66	60
	b	147	100	113	103	116	127	86	98	89
2	a	259	222	234	144	215	121	103	109	67
	b	272	338	206	163	245	111	138	84	67
3	a	84	69	28	25	52	163	134	54	49
	b	100	38	31	44	53	188	71	58	83
4	a	33	45	31	19	32	103	141	97	59
	b	113	41	84	69	77	147	53	109	90
5	a	303	197	125	166	198	153	100	63	84
	b	269	300	203	125	224	120	134	91	56
6	a	125	100	72	125	106	118	95	68	118
	b	84	106	69	72	83	102	128	83	87
7	a	325	228	237	141	233	140	98	102	61
	b	538	453	216	297	376	143	120	57	79
8	a	119	109	65	112	101	118	108	64	111
	b	153	81	69	84	97	158	84	71	87
9	a	84	100	75	34	73	154	119	66	60
	b	63	81	41	66	63	127	86	98	89
10	a	200	216	203	175	199	101	109	102	88
	b	269	269	228	281	262	103	103	87	107
11	a	278	219	162	197	214	130	102	76	92
	b	272	209	172	184	209	130	100	82	88
12	a	128	91	94	63	94	136	97	100	67
	b	128	113	78	75	99	130	115	79	76

* In this column, a indicates May 1, and b, May 3, 1951.
† All counts and levels are for morning hours.
‡ Count as per cent of daily mean.

Venipunctures were performed at 90-minute intervals from 5 to 9:30 a. m. The time consumed in withdrawal of all blood samples at each sampling hour did not exceed 10 minutes. Stasis of the venous blood was minimized by release and reapplication of the tourniquet whenever the first attempt at venipuncture failed. The 5 a. m. sample was obtained with minimal disturbance to sleep. Dormitory lights were not turned on; flashlights were used. The patients remained in their beds, and some of them actually slept until the bell rang, at 6 a. m. The patients were seated for at least two minutes before the 6:30-, 8-, and 9:30-a. m. samples were withdrawn. None of them appeared apprehensive of the venipunctures.

Dried sterile syringes and sharp 20-gauge needles were used. About 5 cc. of blood was withdrawn from each patient on each occasion. Immediately after withdrawal, the blood was transferred to a tube containing dry balanced oxalates and mixed by gently inverting the receptacle for two minutes. The samples were then stored at 10 C. until the time of counting. The

counts were made by the direct method within 12 hours from the time of withdrawal. Certified diluting pipettes, Randolph's diluting fluid,[6] and certified Fuch-Rosenthal counting chambers of 0.2-mm. depth were employed.[7]

Results.—The numbers of eosinophiles per cubic millimeter of blood (absolute eosinophile counts) of a first group, of eight men, at four different times of the same day and on three different days of investigation, are presented in the first section of Table 3. The mean of the four counts for each patient on each day of sampling is shown in the center column. Relative eosinophile levels, expressing each count as a percentage of the day mean, have also been computed and are presented in the right-hand section of Table 1. Comparable data for a second group, consisting of 12 women (tested on two days only) are given in Table 4.

Considerable differences in the eosinophile levels of each patient at the successive sampling times of the same morning are manifested by the absolute counts. In addition, it will be observed from the column of means that large differences exist in the eosinophile levels of different patients, as well as in the levels of the same patient on different days of sampling. An "analysis of variance"[8] was therefore

TABLE 5.—*Analysis-of-Variance Summary for Absolute Eosinophile Counts*

| Group | Source of Variation | D. F. | Variance | F | Significance Levels | |
					0.05	0.01
1 (men).................................	Patients	7	306,388	15.0	2.1	2.9
	Days	2	297,711	14.6	3.1	4.9
	Hours	3	53,438	2.6	2.7	4.1
	Residual	83	20,429	....	...	...
2 (women).............................	Patients	11	58,226	30.5	2.0	2.6
	Days	1	15,100	7.9	4.0	7.0
	Hours	3	26,554	13.9	2.8	4.1
	Residual	80	1,909	....	...	...

undertaken to segregate sources of variation and to examine the significance of the component parts. We present in Table 5 a condensed summary of this analysis, using the pooled interactions (which include the error term) as the residual variance. It will be observed that there are highly significant "patient" and "day" effects in both groups following this procedure. However, the residual variance is too high in Group 1 (men) to allow the "hour-of-day" effect to reach the 5% level of significance.

When the first- and second-order interactions are segregated, and the latter term is used as the residual variance, the "hour-of-day" effect becomes highly significant in both groups. Certain of the first-order interactions also become significant. Detailed consideration of these statistically technical matters seems unwarranted in this paper, which is concerned solely with the simple issues of

6. Randolph, T. G.: Blood Studies in Allergy: The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains, J. Allergy **15**:89 (March) 1944.

7. Two small drops of a 10% aqueous solution of sodium carbonate were added to each 5 cc. of diluting fluid prior to use (according to a suggestion made by Rud [Acta psychiat. et neurol., Supp. 40, 1947] for the use of a different diluting fluid). Two pipettes were used for each sample. The blood was diluted 1 : 10. Four chambers (per sample) were counted.

8. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, Ed. 4, Ames, Iowa, Iowa State College Press, 1946.

main effects. It suffices to demonstrate that differences not only among patients, but also in the eosinophile levels of the same patient on different days, must be major considerations in the design of experiments involving this determination. Indeed, these patient-day effects can be so great as to obliterate the significance of the hourly change in eosinophile levels in a simple analysis.

The primary objective of this investigation has been detection of changes in the number of eosinophiles during the morning hours for persons with mental deficiency. Differences in the eosinophile counts obtained at different hours of the same day and from the same patient are therefore the major point of this paper.

TABLE 6.—*Analysis-of-Variance Summary for Relative Eosinophile Counts*

Group	Source of Variation	D. F.	Variance	F
1 (men)...	Patients	7	0.184*	0
	Days	2	0.045*	0
	Hours	3	11,735	27.3†
	Residual	83	430	..
2 (women).....................................	Patients	11	0.000	0
	Days	1	0.000	0
	Hours	3	13,415	27.4†
	Residual	80	490	..

* Number modification effect only.
† $F_{1\%} = 2.7$.
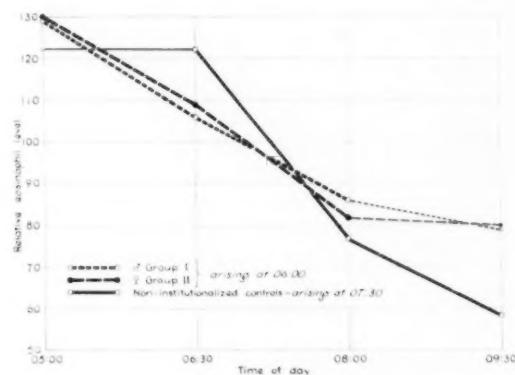
Synchronization of endogenous eosinopenia with initiation of daily activities. Statistically significant changes are represented by heavier lines.

It is to be noted that the subjects of this investigation form a relatively homogeneous group of patients, and that the circumstances of study were standardized to a degree not usually attainable with noninstitutionalized populations. Despite these controls, differences between patients and the effects of day of study have served to obscure hourly changes in the eosinophile level, so that recourse to involved statistical procedure was necessary to demonstrate that an "hour-of-day" effect is present. Moreover, this does not suffice to display its character. It therefore seems desirable to eliminate the person and day effect in the basic data, if possible, so that the primary objective may be reached in clear view of all. For this reason the conversion to relative eosinophile levels was undertaken. This must

eliminate at once all person and day effects, together with person-day interaction, since all such averages are now arbitrarily determined as 100. It is interesting to compare the analysis-of-variance summary, given in Table 6, for the relative eosinophile levels with the corresponding results in Table 5, based on absolute counts.

The "hour-of-day" effect now stands out with unmasked clarity, being highly significant even with a residual of pooled interactions (only one of which is reduced to zero). The merit of conversion of absolute eosinophile counts into relative eosinophile levels for the evaluation of endogenous eosinopenia is thus apparent.

Changes in the mean relative eosinophile level for our two groups of patients are presented graphically in the accompanying Chart. It will be noted that, on the average, there is a substantial decrease in eosinophiles from 5 to 6:30 a. m. ($P_t = 0.001$) and, again, from 6:30 to 8 a. m. ($P_t = 0.004$). These changes are clearly significant, in contrast to the slight change from 8 to 9:30 a. m. ($P_t = 0.206$). The occurrence of endogenous eosinopenia in our subjects is thus defined. In view of the finding that patients with panhypopituitarism and/or adrenocortical insufficiency fail to exhibit endogenous eosinopenia,[1e] these data support the hypothesis of a functioning adrenal cortex in mentally deficient patients of both sexes.

It is of additional interest that the timing of endogenous eosinopenia in the subjects of this investigation differs from that of subjects who are sleeping or resting until later in the morning. Daily activities of these institutionalized subjects have been initiated for years at 6 a. m. This is approximately 90 minutes earlier than the rising time for the subjects of another investigation, by one of us (F. H.).[1e] A hypothesis that endogenous eosinopenia actually occurs earlier in subjects who get up at 6 a. m. than in those who get up later is in keeping with the statistical findings, namely, (a) lack of significance for the change in mean relative eosinophile level from 8 to 9:30 a. m. in subjects who get up at 6 a. m., and (b) lack of change in mean relative eosinophile level from 5 to 6:30 a. m. in subjects who get up at 7:30 a. m.[1e] An inference that decrease in number of circulating eosinophiles is related to initiation of daily activities is appropriate. It is conceivable that the adrenal cortex, which can bring about a decrease in numbers of eosinophiles by an increase in the output of eosinopenic corticoids, is "an exceptionally substantial and durable self-winding and self-regulating physiological clock,"[9] necessary for the synchronization of a metabolic cycle of 24 hours' duration with the regularly recurring changes in the environment.

COMMENT

The earlier literature on eosinophile counts in mentally deficient patients contains only sporadic data on miscellaneous material. It has been reviewed by Rud.[10]

The eosinophile response to epinephrine[11] in mongolism has been investigated recently.[12] No differences were found between normal subjects and patients with

9. Johnson, M. S.: Effect of Continuous Light on Periodic Spontaneous Activity of White-Footed Mice (Peromyscus), J. Exper. Zool. **82**:315 (Nov.) 1939.

10. Rud, F.: Eosinophil Count in Health and Mental Disease: A Biometrical Study, Acta psychiat. et neurol., Supp. 40, 1947.

11. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005 (July 17) 1948; correction **137**:1544 (Aug. 21) 1948.

12. Rothschild, I., and Riepenhoff, J. P.: Circulating Eosinophil Response to Epinephrine in Mongolism, J. Clin. Endocrinol. **12**:480 (April) 1952.

mongolism. The value of the conventional epinephrine test for assessing pituitary-adrenocortical function is obscured by the considerable number of (a) false-positive results (less than 50% fall in number of eosinophiles) in normal subjects given injections of epinephrine at 8 a. m.[13] and of (b) false-negative results (over 50% fall) in patients without demonstrable adrenocortical function. At variance with the epinephrine test, false-negative results (over 20% fall) have not been noted with the endogenous-eosinopenia[3] test.

Differences in the eosinophile counts obtained from the same patient at the same time of day on different days of investigation could be due to changes in the amounts of eosinopenic corticoids[14] secreted in the different environmental circumstances. It is of interest in this regard that considerable changes in the urinary excretion of 17-ketosteroids following a pronounced meteorological change have been reported recently from Zimmermann's laboratory.[15] It is conceivable that an index as sensitive as the eosinophile response could respond to the same, or, perhaps, to smaller, meteorological changes. Yet, whatever the cause of "day" differences in absolute eosinophile counts may be, the demonstration of their high statistical significance calls for caution in attempts to compare absolute eosinophile counts obtained on different days of sampling.

SUMMARY AND CONCLUSIONS

Eosinophile counts were obtained on institutionalized patients with mental deficiency at specified times during the morning hours on several days of investigation. Differences in numbers of eosinophiles among patients, among days of investigation, and among times of day were shown to be highly significant. It is demonstrated that a desirable experimental design will require testing of the same patients on the same days and at the same time of day. Simplification of analysis of data for changes in number of eosinophiles can be achieved by conversion of absolute counts into relative levels.

The data presented demonstrate the occurrence of endogenous eosinopenia in mentally deficient patients of both sexes. If morning changes in number of eosinophiles indicate changes in the rate of secretion of certain adrenocortical hormones, these findings support the hypothesis of a functioning adrenal cortex in the patients studied.

Endogenous eosinopenia is correlated with the initiation of daily activities in a given population. It seems necessary to adapt the schedule of sampling blood for endogenous-eosinopenia tests to the time when daily activities are routinely initiated by the subjects to be tested.

13. Halberg, Cohen, and Flink.[3] Fisher, B., and Fisher, E. R.: Observations on the Eosinophil Count in Man: A Proposed Test of Adrenal Cortical Function, Am. J. M. Sc. **221**:121 (Feb.) 1951.

14. Halberg, F.: Some Correlations Between Chemical Structure and Maximal Eosinopenia in Adrenalectomized and in Hypophysectomized Mice, J. Pharmacol. & Exper. Therap. **106**: 135 (Oct.) 1952.

15. Uters, M.: Hofschlaeger, J.; Anton, H. U., and Zimmermann, W.: Die 17-Ketosteroidausscheidung als Anzeichen für die Beeinflussung des Organismus durch meteorologische Faktoren, Deutsche med. Wchnschr. **76**:1408 (Nov.) 1951.

STUDY OF ADRENOCORTICAL PHYSIOLOGY IN NORMAL AND SCHIZOPHRENIC MEN

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IN PREVIOUS publications [1] we reported data for various measures of adreno-cortical function of schizophrenic and normal men (aged 20 to 39) at rest, when subjected to stress, and when given test doses of corticotropin and adrenal cortex extract by injection. The present study is an extension of these investigations in which we report data reflecting adrenal cortical physiology in two age groups each of normal subjects and of schizophrenic patients.

1. (a) Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74, 1949. (b) Pincus, G., and Hoagland, H.: Adrenal Cortical Responses to Stress in Normal Men and in Those with Personality Disorders: Some Stress Responses in Normal and Psychotic Subjects, Am. J. Psychiat. **106**:641, 1950. (c) Hoagland, H.: Metabolic and Physiologic Disturbances in the Psychoses, Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, p. 434.

MATERIAL AND METHODS

In this study the urinary excretion rates of urinary water, total 17-ketosteroids, creatinine, inorganic phosphates, sodium, potassium, uric acid, and corticoids (neutral reducing lipids) were measured; in addition, in the blood, the lymphocyte and eosinophile count and the sugar content were determined. Methods used in these determinations are cited in references to previous studies.[1a, b]

Seventy-two normal men divided into two age groups of 20 to 39 and 40 to 60 years were studied and compared with 67 schizophrenic men patients at the Worcester State Hospital divided into the same two age groups. In the accompanying Tables and Charts the number of subjects involved and the number of observations made are specifically indicated. It was not possible to obtain complete data on all the subjects in all the tests.

The controls were healthy volunteers obtained from the community at large by contacting church, factory, club, and firemen groups. They came to the Worcester State Hospital for our experiments and were paid for their time. The controls were interviewed by a psychiatrist or a social worker, and those with a history of psychiatric illness were excluded from the study. The patients used all had an illness diagnosed as schizophrenia at the time of the study by psychiatrists at the Worcester State Hospital. In cases of controversial diagnoses the patients were excluded from the tests. Care was also taken to eliminate patients and controls with observable organic illness. No attempt was made to select patients according to the subclasses of schizophrenia.

The hospitalization period for the 20-to-39-year group originally studied averaged $2\frac{1}{2}$ years (range, one month to 11 years). The hospitalization period for the 40-to-60-year group averaged 11 years (range, $1\frac{1}{2}$ to 29 years). We examined our biochemical data in terms of duration of hospitalization and, so far as possible, duration of illness, but found no significant correlations between these factors and adrenocortical responsivity to corticotropin.

The patient and control groups 20 to 39 years of age are the same ones that we reported on in our earlier communications,[1b] and the experimental procedure carried out with the 40-to-60-year groups was similar to that described in our study with the younger groups. Briefly, the procedure was as follows: The subject omitted breakfast on the test day, although he was allowed water ad libitum. On arising in the morning, he voided and started his control collection from the time of this discarded voiding. He did not void again until just before his test, when a sample, timed accurately from the previous discarded voiding, was obtained, corresponding to a two-to-three-hour collection of urine in the bladder. A control sample of venous blood was also then colletced.

Immediately after collection of these control samples of blood and urine, the subject underwent a stress test or received a test injection of 25 mg. of corticotropin (equivalent to 25 mg. of Armour LA-1A or U. S. P. standard). A second blood sample and a second urine sample were obtained 1 hour 15 minutes from the start (zero time) of the stress test, which lasted an hour, or from the time of injection of corticotropin. Three and one-quarter hours from zero time, or two hours later the third blood and urine samples were collected, the subjects remaining relatively inactive during the intervening period. The three samples are referred to as control (prestress), stress, and poststress samples. It is important to note that all collections were made at corresponding times of the day; otherwise, the marked diurnal rhythm of adrenocortical action would have been an additional variable.[2]

Each subject spent four days undergoing tests, the order of which differed for different subjects. The stresses [1b] consisted of four types: 1. A psychomotor test, the subject operating a pursuit meter for an hour. This machine has airplane-type of controls, and its operation is mildly fatiguing. 2. A psychologically frustrating test, the Target Ball Frustration test. This is a kind of pinball game in which the subject, after some practice, is asked to set an aspiration score in terms of what he believes he can achieve in accordance with the scores he has made in

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2. Pincus, G., and Hoagland, H.: Steroid Excretion and the Stress of Flying, J. Aviation Med. **14**:173, 1943. Pincus, G.; Romanoff, L. P., and Carlo, J.: A Diurnal Rhythm in the Excretion of Neutral Reducing Lipids by Man and Its Relation to the 17-Ketosteroid Rhythm, J. Clin. Endocrinol. **8**:221, 1948.

trial runs and in terms of norms set by others. After a practice period, in which he generally achieves his aspiration level, his performance rapidly deteriorates, owing to manipulation of the apparatus by the experimenter unknown to the subject. The psychological build-up of the situation is such as to produce frustration on the part of the subject in the face of his failure to maintain his expected score, and this test also, as in the case of the pursuit meter, mildly activates the pituitary-adrenocortical system. 3. A purely physiological stress test, consisting of the ingestion of sugar by the Exton-Rose technique.[3] 4. Intramuscular injection of 25 mg. of corticotropin, standardized against the Armour LA-1A standard. Each batch of corticotropin sent us by the Armour Laboratories had been assayed by them and expressed as milligrams equivalent of their LA-1A standard. The potencies of the batches varied considerably. The weights of corticotropin that we used for injection were such as to be equivalent to 25 mg. of the standard.

RESULTS

Table 1 shows mean values for prestress (control) urine and blood samples. The figures in parentheses are the total number of determinations, i. e., the product of the number of subjects taking the test and the number of tests per subject. We

TABLE 1.—*Mean Prestress Morning Values of Urinary and Blood Constituents*

	Urine Rate, Cc./ Min.	17-Keto-steroids, Mg./ Hr.	Creatinine, Gm./ 24 Hr.	Urinary PO₄, Mg./ Min.	Urinary K, Mg./ Hr.	Urinary Na, Mg./ Hr.	Uric Acid, Mg./ Min.	Cortins, Mg./ 24 Hr.	Blood Sugar, Mg./ 100 Cc.	Lymphocytes/ Cu. Mm.	Eosinophiles/ Cu. Mm.
Normal subjects, age 20-39..	1.38 (166)	0.54 (153)	1.50 (158)	0.54 (135)	167 (142)	150 (142)	0.51 (155)	3.02 (148)	98.7 (72)	3,068 (175)	... ...
Schizophrenics, age 20-39....	**1.98** (110)	*0.70* (110)	**1.63** (108)	**0.26** (80)	**197** (77)	**306** (76)	0.50 (105)	**2.29** (104)	**91.8** (86)	3,036 (120)	187 (15)
Normal subjects, age 40-60..	0.99 (99)	0.25 (98)	1.36 (102)	0.36 (96)	95 (102)	142 (101)	0.36 (102)	2.51 (91)	97.9 (29)	3,877 (115)	248 (56)
Schizophrenics, age 40-60....	**1.66** (95)	**0.35** (90)	1.49 (94)	**0.22** (91)	**142** (87)	**197** (86)	**0.42** (94)	2.14 (81)	95.8 (35)	3,146 (111)	122 (83)

* Figures in parentheses are number of determinations averaged for the value. Boldface for patients' data indicates a statistically significant difference from the mean of the normal subjects of the same age range at better than a 1% level of significance. Italics indicate a level of significance between 5 and 1%.

have statistical evidence [4] to justify the procedure of averaging together in the same population combined prestress within-man and between-man values as indices of population differences. A statistical analysis of variability of the data obtained from the four groups, i. e., those of younger normal subjects and patients and older normal subjects and patients, was made. A significant within-man and between-man consistency of the data for all four groups was found. The analysis justifies the view that each man has a characteristic level of functioning which we have adequately sampled. The analysis also validates the assumption made in this and in our earlier work that each man may serve as his own control in an assay by percentage changes of the effects of stresses and injections on measures of adrenocortical responsivity. The analysis indicates that we are dealing with a homogeneous set of measurements for each group and that one group is no more variable than another. The variability of the data for the schizophrenic subjects is found to be no greater than is that of the normal subjects.

3. Freeman, H., and Elmadjian, F.: Carbohydrate and Lymphoid Studies in Schizophrenia, Am. J. Psychiat. **106**:660, 1950.

4. Bumer, C.; Ballan, J., and Pincus, G.: Analysis of Variability of Adrenocortical Function Measures in Schizophrenic Patients and in Normal Subjects, unpublished data.

Table 1 confirms and extends our earlier [1b, c] published prestress determinations on the same 20- to 39-year-old patient and normal groups, but is more complete, since only one prestress value per man was previously presented, i. e., the prestress value for the dextrose tolerance test. In the present table, prestress values for this and for the pursuit meter, target ball, and corticotropin tests done on different days, but all at the same time of day (postrising morning samples), are averaged together. Data for the 40- to 60-year groups are presented here for the first time.

Table 1 shows differences with their statistical significance between comparable age groups of normal and schizophrenic men of the variables reflecting aspects of adrenal function. Thus, both the younger and the older groups show differences between schizophrenic and normal subjects in urine volume and in rates of excretion of 17-ketosteroids, inorganic phosphate, potassium, sodium, and "cortins." The lymphocyte level is the same in the two younger groups, but is significantly lower in the older patients than in the older normal subjects. Eosinophiles were not counted in the younger group, but in the older group the level of eosinophiles in the patients was only about one-half that seen in controls of the same age range. This finding confirms the observation reported by others [5] who found lower levels of eosinophiles in schizophrenic patients than in normal controls. The data extend our earlier reports on the 20- to 39-year groups. Because many more observations have been included in Table 1 than in our earlier publications of data on the same younger group, significant differences in 17-ketosteroid and potassium excretion are apparent that were not previously in evidence. The patients excrete more urinary water and more sodium and display a significant reduction in corticoid output. While the corticoids were measured as neutral reducing lipids, we have also shown a comparable reduction in schizophrenic subjects when we measured corticoids as formaldehydogenic steroid [6] either after acid hydrolysis or after treatment of the urine with glucuronidase. The younger schizophrenic patients (Table 1) excreted only 76% of the corticoids of the younger normal subjects, and the older patients excreted 85% of the corticoids of the older normal group ($P < 0.005$ for both differences). These direct measures of corticoids indicate a mild hypoadrenalism in the schizophrenic patients, which is more pronounced in the younger patients. The excessive loss of sodium and urinary water is consistent with this finding, although the patients also tend to lose somewhat more potassium than do the normal subjects. Sleeper [7] reported an excessive passage of urine on the part of schizophrenic patients, similar to that shown in Table 1. This abnormal loss of water and sodium may, of course, involve factors (including psychological factors) other than the adrenal cortex in the patient group. The patients' diuresis may be a result of disturbance of control of water metabolism by the antidiuretic hormone of the posterior lobe of the pituitary, and the loss of sodium and potassium may be a mere flushing out of these electrolytes by the flow of urine. It is of interest, however, that inorganic phosphate is excreted less by the patients than by the controls. This low resting phosphate excretion by the patients is in sharp contrast to their excessive

5. Altschule, M. D.: Discussion, in Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, p. 449.

6. Pincus, G.: Adrenal Function in Schizophrenic Men, Ciba Foundation Symposium, London, 1951, to be published.

7. Sleeper, F. H.: Investigations of Polyuria in Schizophrenia, Am. J. Psychiat **91**:1019, 1935.

excretion of phosphate as compared with that of normal subjects which we have demonstrated [1a] in response to injections of corticotropin, to injection of adrenal cortex extract, and to stress. This phenomenon will be further demonstrated in this paper.

From the data on 17-ketosteroids, one might conclude that the patients have hyperadrenocortical function contrary to the evidence obtained from our direct corticoid measurements. The excretion of 17-ketosteroids of the younger normal subjects is 77% that of the younger patients, and the older normal subjects excrete 72% of the 17-ketosteroids of the 40- to 60-year group. We have previously published evidence [8] that excessive diuresis produced by drinking large quantities of water does not increase the rate of excretion of 17-ketosteroids, so that the patients' diuresis is not a factor in their enhanced output of 17-ketosteroids.

Table 1 shows consistently lower values for all the urinary measures in the older group of normal subjects than in the younger group of normal subjects, and these results are consistent with data we have reported elsewhere.[9] Lower values for these urinary variables in the older schizophrenic group than in the younger schizophrenic group are also seen in Table 1.

The data indicate that schizophrenic patients, as compared with normal subjects, may be deficient in the production of steroids regulating the retention of sodium and are certainly deficient in over-all corticosteroid output. The precursors of 17-ketosteroids, on the other hand, are produced in excess by the patient group.

The low values for resting eosinophiles have been interpreted by Altschule [5] to indicate a continuous overproduction of 11-oxysteroids, but this clearly is not the case, as may be seen from the subnormal corticoid production of the patients in Table 1, confirming our earlier publications.[10] The resting levels of eosinophiles are regulated by various factors, most of which are not understood. The assumption that the low value is due to an over-all excess production of 11-oxysteroids is clearly untenable, although the possibility that an unusual type of eosinophile-lowering steroid may be produced in excess by the patients cannot be ruled out.

Stress Responses of the Adrenal Cortex of Patients and Normal Subjects.—As in our earlier studies of the 20- to 39-year groups of normal subjects and patients, we computed percentage changes in the variables of the urine and blood for each of the three stress tests and for the corticotropin test injections in the 40- to 60-year groups. Data from the prestress samples were arbitrarily assigned values of zero and percentage increases or decreases of the data for the stress and poststress samples were determined for each subject in each test. The mean percentage changes from mean pretest levels of each variable for all the patients was averaged for each test, and a similar averaging was carried out for the normal group.

Chart 1 shows data for the pursuit meter test averaged for 25 controls and 17 patients in the 40- to 60-year groups. In this Chart, and in Charts 2, 3, and 4, the impact of the stress or injection on each variable is seen in terms of the height

8. Pincus, G.: Diurnal Rhythm in the Excretion of Urinary Ketosteroids by Young Men. J. Clin. Endocrinol. **3**:195, 1943.

9. (a) Pincus, G.: Measures of Stress Responsivity in Younger and Older Men. Psychosom. Med. **12**:225, 1950. (b) Pincus, G.; Romanoff, L. P., and Carlo, J.: Urinary Steroid Excretion in Relation to Age, J. Gerontol. (Supp.) **6**:135, 1951.

10. Pincus and Hoagland.[1b] Pincus.[9]

above the base line of the appropriate rectangle.[11] The first rectangle of each pair corresponds to data from the stress sample collected immediately after the test, which lasted one hour, or an hour after injection of corticotropin. The second rectangle of the pair corresponds to data from the poststress sample collected $2\frac{1}{4}$ hours later ($3\frac{1}{4}$ hours from zero time). The vertical length of the rectangle is the percentage change from zero, the mean of the prestress, or preinjection, samples. Vertical hatching denotes statistical significance at a level of between 5 and 1% of differences between normal subjects and patients for a particular variable, and diagonal hatching indicates significance at less than the 1% level. Open columns indicate that differences between patients and controls are not significant at less than 5% levels of confidence. An open circle above a rectangle indicates statistical
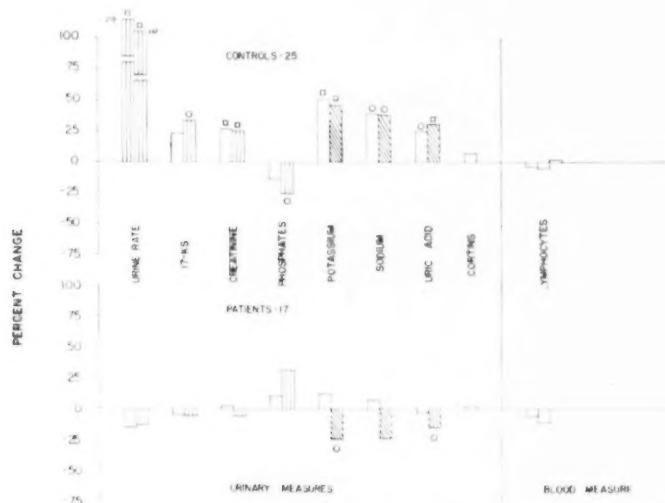
Chart 1.—Comparison of responses of 40-to-60-year-old normal men and schizophrenic men in the pursuit meter test. For description of the chart and its discussion, see text.

significance of change from the prestress level of between 5 and 1%; a square over the rectangle denotes significance at less than the 1% level. Columns with no designations over them indicate changes from control levels greater than 5% levels of confidence. These statistical criteria are used also in Charts 2, 3, and 4. This method of plotting is similar to that used in our earlier studies of the younger groups.[1b] In some of the four charts blood data are presented by three rectangles. The first two rectangles correspond to venous blood samples taken at the time of taking the stress and poststress samples of urine. The third rectangle, when it occurs, corresponds to a blood sample taken one hour after the poststress urine sample ($4\frac{1}{4}$ hours from zero time).

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11. The mean basal data are shown in Table 1, and Charts 1 to 4 show percentage changes from these basal values. Space limitation has made publication of the actual data impractical. In an earlier paper [1a] we published tables of data for most of the 20-39 age groups of patients and normal subjects, and the reader is referred to this paper. These tables, comprising 10 journal pages, represent less than one-half the data analyzed in this paper.

The control samples were early morning samples taken when the adrenal output was maximal after rising. We [2] have shown that there is an increase of approximately 50% in adrenocortical output in normal young men during the first two hours after waking, and in the absence of stress the output progressively declines during the day, with minimal output again at night. The control samples thus correspond to periods of maximal diurnal output, and if a given stress is ineffective, the signs of percentage change in adrenocortical function will be negative (below zero) in the case of the urinary variables (other than creatinine) and positive (above zero) for lymphocytes and eosinophiles. This follows since the stress and poststress samples occur later in the day (by one and three hours respectively), at a time of lower adrenal activity due to the diurnal rhythm.
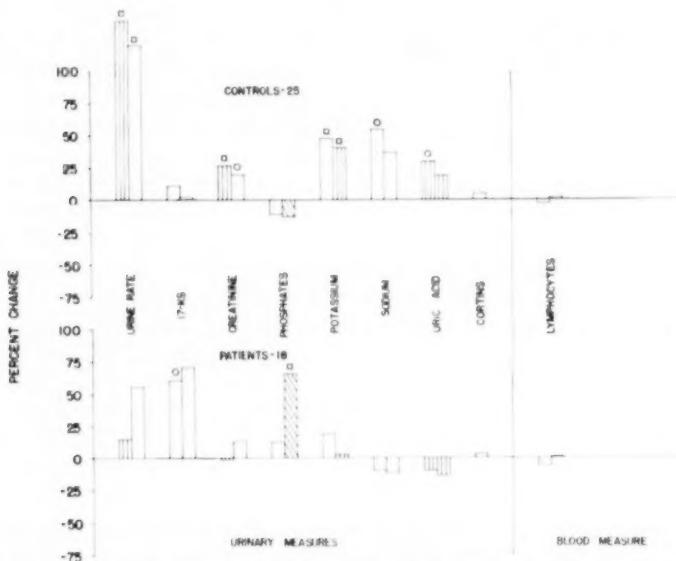
Chart 2.—Comparison of responses of 40-to-60-year-old normal men and schizophrenic men in the Target Ball Frustration test. For description of chart and its discussion, see text.

Comparison of data for 17 patients and for 25 controls in the pursuit meter test in Chart 1 confirm most of our experiences with the younger age groups.[1b, c] The adrenal cortex of the patients is less responsive. The normal subjects respond by significantly increased output of urinary water, 17-ketosteroids, potassium, sodium, and uric acid and a significant ($P < 0.05$) fall in rate of excretion of urinary phosphates in the poststress sample. The corticoids and lymphocytes show no significant changes. The patients are comparatively unresponsive. Significant changes in potassium and uric acid excretion are in a direction opposite that seen in the normal group, and there is an increased excretion of phosphates. It is clear from the rectangles with hatching that the two groups differ significantly in most of the changes.

Responses to the Target Ball Frustation test are shown in Chart 2 for 18 patients and 25 normal subjects. This stress test also shows significant differences

indicating greater responsivity of the normal group in most of the variables. In both Chart 1 and Chart 2 note should be made of the changes in phosphate excretion. The percentage response of phosphates is much greater in the patients, despite the fact that their resting phosphate excretion is considerably lower than that of the normal subjects (Table 1). The mechanism of this phenomenon is obscure. Again, it is evident that the percentage changes in cortins and in lymphocytes do not differentiate the two older age groups, and this is in accordance with our previous findings in the younger age groups. While the percentage increase in corticoid output is the same in the patient and the normal groups, the absolute output is less in the patients, since the resting basal titer is less.

The data from the oral dextrose tolerance test for 31 patients and 26 normal subjects are seen in Chart 3. In this Chart we include eosinophile data, which show
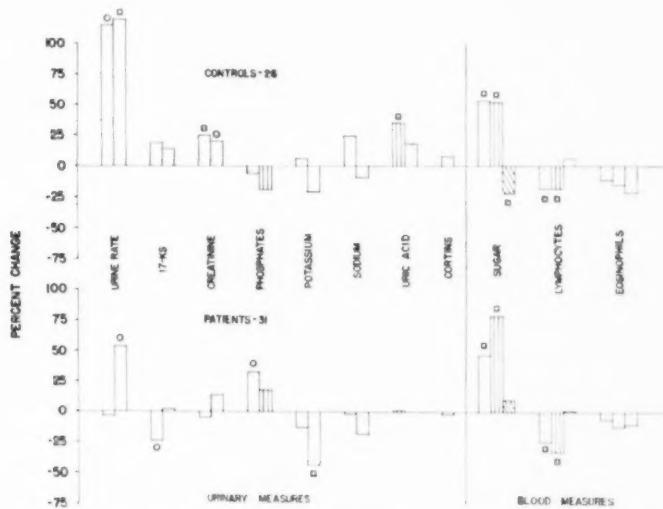
Chart 3.—Comparison of responses of 40-to-60-year-old normal men and schizophrenic men in the oral dextrose tolerance test. For discussion see text.

no group-response differences. If anything, the patients show slightly greater (but not significant) responsivity in lymphocytes, and the poorer dextrose tolerance of the patients is also in evidence from the blood sugar data. These results are in agreement with our earlier findings.[1b, c] The urinary data show significance (at the 5% level) only in poststress changes in phosphates and in stress changes in uric acid excretion. The younger groups showed more response differences in the various urinary measures than this older group in terms of the oral dextrose tolerance test.[3] Chart 3 shows that the normal subjects were more responsive to the test than the patients as measured by urinary variables, but the differences are small and for the most part not statistically significant.

Chart 4 shows the response of 28 patients and 26 normal subjects to test injections of 25 mg. of corticotropin. Here, again, a striking increase in excretion of phosphates in the patients differentiates them as a group, at the 1% level of con-

fidence, from the normal subjects, who show no significant increase in phosphate excretion, though the expected fall due to the diurnal rhythm is eliminated by the corticotropin. The controls show considerably more responsivity than do the patients in potassium and uric acid changes, and the striking increase in phosphate excretion is in sharp contrast to its lack of response in the controls. All other variables fail to differentiate the two groups. In the younger (20-to-39-year) age groups we demonstrated marked differences in favor of greater responsivity of the normal subjects in excretion of 17-ketosteroids and sodium. But in our younger groups we also found no group differentiation in responses of lymphocytes or corticoids to injections of 25 mg. of corticotropin. Chart 4 shows clearly that neither lymphocyte nor eosinophile changes differentiate patients and normal subjects in response to test injections of corticotropin.
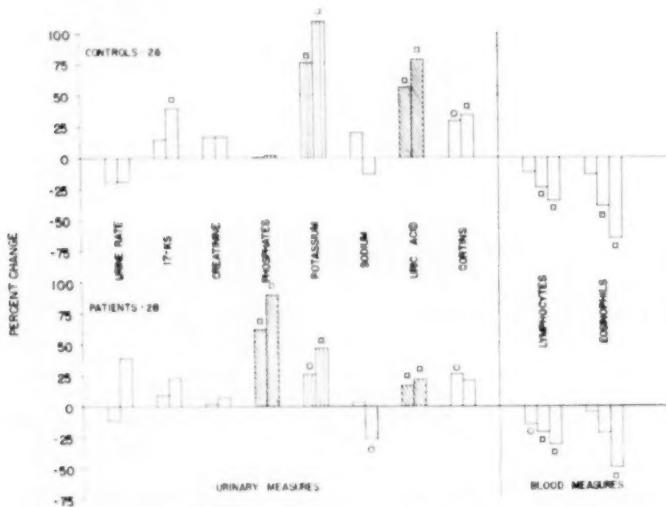
Chart 4.—Comparison of responses of 40-to-60-year-old normal men and schizophrenic men to the injection of 25 mg. of corticotropin (Armour LA-1A standard or U. S. P. standard). For discussion see text.

The four Charts confirm the results we obtained with our younger groups; i. e., the patients are in general less responsive than normal subjects in terms of changes in rates of excretion of urinary 17-ketosteroids (except in the target ball test), potassium, sodium, and uric acid. The differences, however, are not as clear-cut as those found in the younger groups. Perhaps the most consistently challenging patient-control group difference, also previously observed in the younger age groups, is that of the changes in phosphate excretion.

Comparison of Younger and Older Groups by the Total Response Index of the Adrenal Cortex.—We have described a total response index of adrenocortical [1a, b] function. This is constructed by adding the stress and poststress mean percentage changes in 17-ketosteroids, sodium, potassium, uric acid, and corticoids and twice the mean decrease in lymphocytes. Other variables shown in the four Charts are

not included in the total response index, since this index as originally used on the 20-to-39-year group did not incorporate these factors. In our study of this younger group we found, after the test injection of 25 mg. of corticotropin, that each value of this index for each of 25 normal men amounted to +20 or more. A comparable number of patients gave values usually considerably less than normal subjects. Thus, for example, while 100% of 25 normal subjects gave total response indexes of 20 or greater, only 28% of 25 schizophrenic patients gave values of 20 or greater. An increase in total response index of 20 was accordingly defined as a minimum positive response in this test, since all normal subjects attained this minimum level. The three stress tests—pursuit meter, target ball test, and oral dextrose tolerance test—showed that about two-thirds of the patients gave subnormal responses (total response index < 20) as compared with the responses of the group of normal controls.

Tables 2 and 3 show group comparisons in terms of the total response indexes. Columns I, II, III, and IV of Table 2 and Column I of Table 3 show the data for

TABLE 2.—*Total Adrenal Response Index (TRI) of Patients and Normal Subjects of Two Age Groups (20-39 Years and 40-60 Years) Each**

Tests	Normal Subjects, Aged 20-39 Yr.		Patients, Aged 20-39 Yr.		Normal Subjects, Aged 40-60 Yr.		Patients, Aged 40-60 Yr.	
	I TRI Values	II Score of 20 or Greater, %	III TRI Values	IV Score of 20 or Greater, %	V TRI Values	VI Score of 20 or Greater, %	VII TRI Values	VIII Score of 20 or Greater, %
Corticotropin injection, 25 mg.	46.2 (25)	100.0	12.0 (25)	28.0	54.6 (25)	92.0	30.1 (27)	63.0
Pursuit meter	22.1 (46)	47.8	− 2.7 (36)	15.8	38.3 (24)	62.6	4.0 (17)	17.7
Target ball	11.5 (36)	32.5	− 6.7 (29)	10.0	30.9 (24)	62.0	− 6.9 (19)	5.3
Oral dextrose tolerance	22.1 (47)	48.6	5.7 (38)	15.0	29.5 (25)	64.0	3.9 (29)	21.7

* Numbers in parentheses refer to number of subjects averaged for each of the four tests. Significance of TRI differences between patients and controls in the 40-to-60-year group are designated as follows: $P < 0.001$, by boldface; $P < 0.005$, by italics. Analysis of TRI variance was not applied to the 20-to-39-year groups. Presumably, comparable significances of differences would apply.

our younger groups of normal subjects and patients, as previously published.[1b] They are reproduced here for purposes of comparison with the data for the older groups. In terms of responses, the younger normal group show the largest total response scores to the corticotropin test and about half this response score to both the pursuit meter test and the dextrose tolerance test. The target ball test produces only about one-fourth the response in terms of total response score as that of the corticotropin test (Table 2, Column I).

The younger patients show the same order of responsivity to the tests (Table 2, Columns II and IV), but for all tests they are less responsive than the normal subjects of the same age group, in about the same proportion from test to test. This may be seen in Table 3, Column I, in which the ratio of normal responders to schizophrenic responders is approximately 3:1 for all tests when a response is defined as an increase in total response index of 20 or more. The ratio is obtained by dividing the values in Column II (Table 2) by those of Column IV for each test. In the younger patient group the target ball and pursuit meter tests give negative total response values (Table 2, Column III), indicating that the effect of diurnal rhythm was not brought above the base line by these stresses.

The older groups show a somewhat different pattern. The total response values for the older normal subjects are slightly higher than those for the younger subjects (Table 2, Column V); and while the corticotropin test is again the most effective, the other three tests are all about equal as stresses and in the normal subjects are about three-fifths as effective as is the injection of 25 mg. of corticotropin. While corticotropin produces total response indexes of 20 or more in 92% of the older group of normal subjects (in contrast to 100% of the younger normal group), it gives a comparable response in 63% of the older patients (in contrast to 28% of the younger patients). The ratio of older normal responders to older patient responders is 1.5 (Table 3, Column II), in contrast to 3.6 from the younger groups. This figure and the total response indexes of 30.1 and 12.0 from Table 2 for the older and younger patients respectively show that the older patients are considerably more responsive to corticotropin than are the younger patients. Total response indexes for the older patients are about the same as those of the younger patients in the three stress tests (Columns III and VII, Table 2).

TABLE 3.—*Ratio of Responders to the Four Adrenal Response Tests**

	Normal/Schizophrenic Responders		Younger/Older Responders	
	I	II	III	IV
Test	20-29 Yr. Groups	40-60 Yr. Groups	Normal Subjects	Patients
Corticotropin, 25 mg	3.6	1.5	1.1	0.45
Pursuit meter	3.0	3.5	0.76	0.89
Target ball	3.3	12.0	0.52	1.9
Oral dextrose tolerance	3.2	3.0	3.2	0.69

* A responder is defined as one who gives an increase in the total response index in the designated test of 20 or more.

A comparison of Columns I and II in Table 3 shows marked differences in the ratios of normal to patient responders in the two age groups. Instead of being relatively constant for all tests, as in the younger groups, this ratio varies considerably from test to test in the older populations. Thus, the ratios are approximately the same as those for the younger groups in the pursuit meter and dextrose tolerance tests, i. e., about three normal responders to one schizophrenic responder. But the older patients are again seen to be more responsive to corticotropin than the younger patients, as is indicated by a ratio of 1.5 for normal responders to patient responders. The ratio of 12.0 of the target ball test is also very different from that for the younger group. The total response indexes for younger and older patients are the same, 6.7 and 6.9, but there is a high percentage (62) of older normal responders and a low percentage (5.3) of older patient responders to this test, thus accounting for the high ratio. It is as though the frustration of this test was more challenging to the older normal subjects than it was to the younger normal subjects (or to the patients). The total response index for the target ball test is nearly three times as high for the older normal subjects, 30.9, as for the younger group, 11.5. A comparison of ratios for younger to older responders is shown in Table 3, Column III, confirming our earlier findings that the older normal subjects are about as responsive to corticotropin as the younger normal subjects (ratio, 1.1). There are relatively more adrenal responders to the pursuit meter test among the

older group and about twice as many responders to the target ball test in this group. One is tempted to consider that these two tests call more upon reserves requiring adrenal cortical assistance in the older group of normal subjects. The dextrose tolerance test indicates that the responsivity of the younger normal subjects is in approximately a 3:1 ratio to that of the older normal subjects.

<div align="center">COMMENT</div>

The extensive data of Table 1 show statistically significant differences between schizophrenic patients and normal subjects in several measures relevant to adrenocortical function. The high output of 17-ketosteroids and the low output of corticoids suggest a qualitative disturbance in adrenal-steroidogenesis in the patients. Precursors of 17-ketosteroids appear to be produced in excess, but neutral reducing lipids (adrenal steroids) are excreted to a less than normal degree. The high rate of sodium output is, of course, consistent with the latter finding, although, as has been mentioned, factors other than those of the adrenal cortex may be involved.

The study of the 40-to-60-year groups of patients and normal subjects confirms our finding in the younger groups that the patients' adrenal responses to stress are subnormal. The response ratios of the normal subjects who give a total response index of 20 or more to the response ratios of the patients who meet this standard is approximately 3:1 for the pursuit meter and dextrose tolerance tests, as it is for the younger groups.

It is seen that 63% of the older patients give a total response index of at least 20, and a mean total response index of 30.1, to 25 mg. of corticotropin. This is in contrast to the younger group of patients, of whom only 28% are responders and who give a mean total response of only 12.0. The older patients are thus about twice as responsive to injected corticotropin as are the younger patients. Since the total response values for the three stress tests are about the same for the two groups of patients, one is led to consider the possibility that the adrenal stress response deficiency in the older patients may be at the level of the central nervous system or the pituitary, in contrast to that in the younger group, in which it is clearly at the level of the adrenal cortex itself. The last conclusion follows from our original comparison of the younger patient and normal groups, since (*a*) the two groups were equally responsive to injected adrenal cortex extract,[1b] indicating normal steroid metabolism and target-organ response to the steroids following secretion from the gland, and (*b*) injected corticotropin showed the same relative unresponsivity of the patients that was seen after the action of their own pituitary adrenocorticotropic hormone secreted as a result of the stresses of pursuit meter, target ball, and oral dextrose tolerance tests. Thus, the younger patients and the younger controls show quantitatively the same order of adrenal unresponsivity both to endogenous and to exogenous corticotropin, as may be seen from the first four columns of Table 2 and from Column 1, Table 3, in which the ratio of normal responders to patient responders is approximately the same in all four tests (about 3:1). Since injected corticotropin is a specific test of the adrenocortical response per se, we concluded that the subnormal stress responses lay specifically at this level of steroidogenesis by the adrenal cortex. The older patients were considerably more responsive to injected corticotropin than were the younger patients and were about as unresponsive to the stress tests. This indicates that their subnormal

responsivity to stress may reside at a more cephalad level, i. e., in a depressed level of corticotropin release from the pituitary following stress activation of the hypothalamus or in the release of a less effective pituitary adrenocorticotropic hormone than the injected corticotropin.

It is tempting to speculate on the relatively greater unresponsitivity to corticotropin in the younger patients than in the older patients. The younger group contains more acute cases, and it is possible that depressed corticotropin responsivity may be an accompaniment of the more acute psychoses, corresponding to a stage of exhaustion of the adaptation syndrome. The older, more chronic patients, who are better "adjusted" to their psychoses, may show some recovery of responsivity to corticotropin. On the other hand, it is possible that the relative unresponsivity of the younger patients may be genetically determined and be a predisposing factor in the development of the psychosis, thus accounting for the higher incidence of schizophrenia in the younger population. Responsivity to corticotropin may increase slowly with the age in this group, and this may be a factor in the spontaneous remission sometimes encountered in older patients. In this connection it is interesting to note that the older patients excrete comparatively more corticoids than the younger patients. From Table 1 we have seen that older patients excrete 85% of the corticoids excreted by older normal subjects, while the younger patients excrete 76% of the corticoids produced by the younger normal subjects. Finally, a third possibility should be considered. We have reported the rapid inactivation of corticotropin by enzymes in the blood of different animals, including man.[12] Young schizophrenic patients may have a larger concentration of this inactivating enzyme system than older schizophrenic patients. This matter is now under investigation.

Hemphill and Reiss,[13] in England, and Faurbye, Vestergaard, and associates,[14] in Denmark, from studies of urinary constituents have confirmed our earlier findings of reduced adrenal responsivity to stress of schizophrenic patients. The results of these independent investigations are consistent with the findings we have previously reported and with those of this paper.

At no time have we found eosinophile responses to differentiate schizophrenic patients and normal groups, and this is clear from Charts 3 and 4. Hiatt and associates,[15] finding no differences between psychotic patients and normal subjects in eosinophile responses to injected 25-mg. doses of corticotropin, implied that this indicated normal adrenal responsivity in the patients, in contradiction to our studies, in which other signs of adrenal function were used. In our published data [1b.e] on the 20-to-39-year groups of patients and normal subjects, we clearly showed that no group differences exist in lymphocyte responses to 25 mg. of corticotropin or to the target ball, oral dextrose tolerance, and pursuit meter tests. We certainly did

12. Pincus, G.; Hopkins, T. F., and Hechter, O.: An ACTH-Inactivating Factor in Mammalian Blood, Arch. Biochem. **37**:408, 1952.

13. Hemphill, R. E., and Reiss, M.: ACTH in Psychiatry, read at the International Congress on Psychiatry, Paris, Sept. 18-27, 1950.

14. Faurbye, A.; Vestergaard, P.; Kobbernagel, F., and Neilson, A.: Adrenal Cortical Function in Chronic Schizophrenia (Stress, Adrenaline-Test, ACTH Test), Acta endocrinol. **8**:215, 1951.

15. Hiatt, H. H.; Rothwell, W. S., and Horwitt, M. K.: Eosinopenia Produced by ACTH in Patients with Schizophrenia, Proc. Soc. Exper. Biol. & Med. **79**:707, 1952.

not conclude that therefore there were no adrenal response differences, since such differences were clearly manifested by the data on urinary excretion.

The eosinophile count is an unreliable measure of adrenal responsivity in man. Thus Thorn, whose experience with this responsivity test (the Thorn test) is most extensive, stated:[16]

We have observed in certain patients with Addison's disease, and more recently in patients with complete bilateral adrenalectomy, that epinephrine may cause a marked fall in eosinophils . . . . I feel that every statement in which adrenal activation is measured only by an eosinophil fall needs qualification.

We wish to emphasize that there is general agreement that changes in eosinophiles following stress and injection of corticotropin and of epinephrine do not differentiate between psychotic and normal persons. The eosinophile changes that occur tell one little about adrenal cortex physiology.

In earlier experiments, we found pronounced group differences in lymphocyte responses between small groups of normal and schizophrenic subjects when subjected for 45 minutes to temperatures ranging from 105 to 112 F. and a relative humidity of 85 to 95%.[17] We also found similar differences in lymphocyte responses to the continuous operation of the pursuit meter with added anoxia [18] but not to operation without anoxia,[1b] although in the latter case the urinary indices, but not the lymphocytes, were clearly delineative of group differences. Both these stresses, pursuit meter with anoxia and heat with high humidity, were very severe, especially the latter.

Stein, Ronzoni, and Gildea,[19] using a heat stress of 106 F. for 45 minutes, were unable to find group differences when the eosinophile count was used as a measure of adrenal response. There are two major differences in procedure in the St. Louis and Worcester studies. Gildea and associates [19] measured eosinophile changes, while we measured lymphocyte changes, but of probably more significance is the difference in intensity of the stresses involved. Our subjects sat in a room in which the temperature was controlled and a humidifier determined the moisture content of the air. The St. Louis workers used a heat cabinet, with the head exposed. The high water saturation of the respired air in our studies greatly increased the stress, since water could not be eliminated from the lungs. Freeman and Rodnick [20] showed that breathing warm, saturated air is exceedingly stressful, even with the body exposed to normal room conditions. When loss of heat and moisture from the lungs was blocked, as was done in our tests, the stress was much greater than occurs from heating the body with the head exposed, even though the air around the trunk may have been humid.

16. Thorn, G. W.: Transactions of the 3d Conference on Adrenal Cortex (1951), New York, Josiah Macy Jr., Foundation, 1952, p. 66.

17. Pincus, G., and Elmadjian, F.: Lymphocyte Response to Heat Stress in Normal and Psychotic Subjects, J. Clin. Endocrinol. **6**:295, 1946.

18. Hoagland, H.; Elmadjian, F., and Pincus, G.: Stressful Psychomotor Performance and Adrenal Cortical Function as Indicated by the Lymphocyte Response, J. Clin. Endocrinol. **6**:301, 1946.

19. Stein, M.; Ronzoni, E., and Gildea, E. F.: Physiological Responses to Heat Stress and ACTH of Normal and Schizophrenic Subjects, Am. J. Psychiat. **108**:450, 1951.

20. Freeman, H., and Rodnick, E. H.: Autonomic and Respiratory Responses of Schizophrenic and Normal Subjects to Changes of Intra-Pulmonary Atmosphere, Psychosom. Med. **2**:101, 1940.

Neither we nor the St. Louis group have found differences between patients and normal subjects in eosinophile responses to test injections of corticotropin. Gildea and his collaborators [19] quoted from a paper by Hemphill and Reiss [13] indicating disagreement with our findings in relation to adrenal stress responsivity of normal and schizophrenic patients. No disagreement now exists. Dr. Reiss has stated that their work fully confirms our findings with regard to depressed adrenal stress responsivity in schizophrenic patients.[21]

Relative (percentage) changes in corticoids (neutral reducing lipids) following our three standard stresses and after injection of corticotropin also do not differentiate between normal persons and schizophrenic patients. This is clear from the Charts in this paper and from the data of our previous publications for the younger group of patients and controls.[1b] Thus, percentage changes in lymphocytes, eosinophiles, and corticoids following stress and corticotropin injections are the same in normal and in schizophrenic patients, although the absolute levels of output of corticoids in the urine and of resting levels of eosinophiles are significantly lower in the patients (Table 1). The group-differentiating. factors in the stress and corticotropin studies are in terms of excretion of 17-ketosteroids, sodium, potassium, uric acid, water, and phosphate in response to both endogenous and injected corticotropin. This is consistent with the view of qualitatively abnormal steroidogenesis by the schizophrenic patient's adrenal cortex and is especially clear in the data for our younger groups.[1b]

Recent chromatographic studies in our laboratory of specific urinary steroids (unpublished) have demonstrated 35 substances in normal urine, only a few of which are as yet fully identified, although some information about the structural properties of the molecules of many of them has been established. A comparison of chromatograms of normal subjects and those of a small group of schizophrenic patients suggests that several of these compounds are very differently distributed in the two groups. A continuation of this analysis may or may not demonstrate significant group differences of potent steroid constituents.

The activity of steroids determined by bioassays may vary enormously with minor changes in molecular structure. Thus, Tait and his collaborators [22] reported the existence of a steroid in adrenal cortex extract present in trace amounts which is 20 times as active as desoxycorticosterone in its effects on electrolyte regulation. The physiological action of such substances may bear little relation to their relative concentrations in body fluids. It is possible that small amounts of potent steroids, if characteristically produced by the adrenals of psychotic patients, may directly or indirectly modify the action of the central nervous system.

C. H. H. Branch and E. L. Bliss, of the University of Utah, at a recent conference of the Scottish Rite Committee for Research on Dementia Praecox, reported that increases in the amount of hydrocortisone (Compound F) following corticotropin injections were the same in samples of systemic blood taken from normal and from schizophrenic subjects. These results are consistent with our findings that percentage increases in total urinary corticoids following corticotropin injections

21. Reiss, M.: Statement in discussion on a paper read at the 1952 meeting of the American Psychiatric Association.

22. Grundy, H. M.; Simpson, S. A., and Tait, J. F.: Isolation of Highly Active Mineralcorticoid from Beef Adrenal Extract, Nature 169:795, 1952.

do not reflect differences between schizophrenic patients and normal persons. The Porter-Silber method used by the Utah group for determining hydrocortisone measures other steroids containing 17-hydroxy, 21-hydroxy, and 20-ketonic groupings. These include cortisone (Compound E), Reichstein's Compound S [Δ^4-pregnene-17(β):21-diol-3:20-dione], tetrahydrocortisone, tetrahydrohydrocortisone, Reichstein's Compounds V[*allo*pregnane-3(β):11(β):17(β):2-tetrol-20-one], C[Kendall's Compound C, or *allo*pregnane-3(a):11(?):21-tetrol-20-one], P [*allo*pregnane-3(β):17(β):21-triol-20-one], and several other possible isomers of these substances. The possibility of aberrant steroidogenesis in psychotic patients within this group of compounds, and, perhaps even more significantly, within other non-alpha-ketol fractions containing many other steroids remains to be determined in detail.

SUMMARY

Various indices of adrenal cortex function in normal men and schizophrenic men at rest and when subjected to three stress tests (oral dextrose tolerance, pursuit meter and Target Ball Frustration tests) and to the injection of 25-mg. test doses of corticotropin are described.

The normal and psychotic groups were divided into younger (20 to 39 years) and older (40 to 60 years) groups. These four groups were studied statistically as separate populations.

In both the older and the younger groups the schizophrenic patients at rest showed a significantly higher rate of excretion of urinary water, 17-ketosteroids, sodium, and potassium than the normal subjects. They showed lower than normal rates of excretion of corticoids and phosphates and thus displayed at rest evidence both of hyperadrenalism and of hypoadrenalism.

Confirming our earlier work with patients and normal subjects of the younger age group, we found that the older patients showed less adrenal response to the stress tests and to injected corticotropin than the older normal subjects. The total response index of the adrenal cortex was used in these comparisons. As in our earlier studies of the younger groups, it was the urinary 17-ketosteroids, sodium, potassium, uric acid, and inorganic phosphates that reflected these group differences. Percentage changes in eosinophile and lymphocyte levels and percentage changes in corticoid excretion, as we have previously reported, did not differentiate statistically between normal and schizophrenic populations in the four tests we used.

The older schizophrenic patients, while about as unresponsive to our three stress tests as the younger schizophrenic patients, were considerably more responsive to corticotropin than were the younger patients.

The experimental findings are discussed in terms of possible underlying mechanisms and in terms of their possible relation to the etiology of schizophrenia.

SUBDURAL HEMATOMA FOLLOWING SUBARACHNOID HEMORRHAGE

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IN THE recent literature dealing with spontaneous subarachnoid hemorrhage and the surgical treatment of intracranial aneurysms, there is little or no recorded experience with the finding of associated subdural hematoma. That these two hemorrhagic processes may originate in a common bleeding episode has been recognized by Dott,[1] Helpern,[2] and Jaeger.[3] Recognition of this possibility will suggest, in cases of subdural hematoma without evidence of traumatic origin, a search for well-known sources of subarachnoid bleeding. On the contrary, in cases of subarachnoid hemorrhage followed by certain unusual developments, the presence of a subdural hematoma may be suspected.

Of our series of 334 cases of proved subarachnoid hemorrhage of nontraumatic origin,[4] a subdural hematoma was discovered in 13. In each case the age of the subdural hematoma, as judged by the degree of clot organization or membrane formation, corresponded with the time lapse after a definite bleeding episode. Of the 13 cases, the cause of subarachnoid bleeding was ruptured arterial aneurysm in 7, extension of spontaneous intracerebral hematoma in 3, massive intracerebral hemorrhage occurring in toxemia of pregnancy in 1, and an undetermined factor in 2. Of the seven cases of aneurysm, the location of the bleeding aneurysm was at the bifurcation of the internal carotid artery in three, at the junction of the internal carotid and posterior communicating arteries in two, and on the anterior cerebral artery distal to the origin of the anterior communicating artery in two. In two of the seven cases of bleeding aneurysm there was associated intracerebral hematoma. In this report, we are concerned mainly with those cases in which subdural hema-

1. Dott, N. M.: Intracranial Aneurysm: Cerebral Arterio-Radiography; Surgical Treatment, Tr. Med.-Chir. Soc. Edinburgh 40:219-240, 1933.

2. Helpern, M.: Multiple Saccular Aneurysms of the Cerebral Arteries: Rupture into the Subdural Space, Proceedings of the New York Pathological Society, May 26, 1933, p. 46; Arch. Path. 16:754-756, 1933.

3. Jaeger, R.: Aneurysm of the Intracranial Carotid Artery: Syndrome of Frontal Headache with Oculomotor Nerve Paralysis, J. A. M. A. 142:304-310, 1950.

4. Odom, G. L.; Bloor, B. M.; Golden, J., and Woodhall, B.: Acute Subarachnoid Hemorrhage: Etiology and Prognosis, North Carolina M. J. 13:624-627, 1952.

toma originated from the rupture of an intracranial aneurysm. In the cases of subdural hematoma arising from direct extension of intracerebral hemorrhage, whatever the cause, the fact that the hematoma exists both within the brain and in the subdural space is of little significance from the diagnostic point of view. In terms of prognosis, nothing can be concluded from the present small series; one can only point out that since operation was followed by recovery in all three cases of spontaneous intracerebral hematoma with subarachnoid and subdural extension, the mortality tended to be no higher than in a much larger series of cases of intracerebral hematoma, uncomplicated by subdural hematoma, surgically treated by Odom, Bloor, and Woodhall.[5] Because of the spatial separation of the two processes, the relation of subdural hematoma to aneurysm is much more likely to be overlooked. This is especially true if the symptoms and signs of an intracranial mass obscure the usual clinical features of subarachnoid hemorrhage, as occurred in one of our cases, to be mentioned below.

Subdural hematoma was not suspected in any of these cases before operation or autopsy. Displacement of the ventricles in the ventriculogram or displacement of arteries in the arteriogram was assumed to be due solely to intracerebral hematoma. In retrospect, what were the unusual clinical features that might have led one to suspect concurrent subdural hematoma? In only one case was the general clinical course different from that which would be expected to follow subarachnoid hemorrhage. In this case, in which there was a five-month history of progressive headache, vomiting, and seizures and the only abnormal findings were bilateral papilledema and unilateral preretinal hemorrhage, the history of a typical episode of subarachnoid bleeding was obtained only after an encapsulated subdural hematoma had been removed. An arteriogram then revealed an ipsilateral aneurysm at the bifurcation of the internal carotid artery; this showed definite evidence of previous bleeding at operation.

A striking feature of the cases of aneurysm was the high incidence of retinal hemorrhage. In three of these cases a subhyaloid hemorrhage ipsilateral to the aneurysm and subdural hematoma was observed. In three others retinal hemorrhages developed immediately after the second subarachnoid hemorrhage, and in two of these cases the retinal hemorrhages were seen in the ipsilateral eye only. Although subhyaloid hemorrhage has often been considered a frequent accompaniment of subarachnoid hemorrhage, it was present in only 4 of the other 321 cases of subarachnoid hemorrhage from which this series was taken, and unilateral retinal hemorrhage, in 11. Intracerebral hematoma was present in three of these cases and may have contributed to obstruction of venous drainage. However, in 51 other cases of large hemisphere hematomas, there were only 7 instances of retinal hemorrhage, and in none of these was it subhyaloid.

Although no conclusions can be drawn from this small series, the prognosis in cases of subdural hematoma following subarachnoid hemorrhage tends to be essentially no different from that in cases in which there is no subdural hemorrhage. Of the three cases of aneurysm treated surgically, good recoveries occurred in two, and postoperative thrombosis of the internal carotid artery was the cause of death in the third.

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5. Odom, G. L.; Bloor, B. M., and Woodhall, B.: Intracerebral Hematoma: A Survey of 106 Verified Cases, South. M. J. **45**:936-942, 1952.

The high incidence of unilateral ocular hemorrhage in these cases appears to be of significance. Several explanations of the development of this phenomenon appear in the literature.[6] It seems fairly well established that, although the subarachnoid and subdural spaces of the optic nerve sheath are continuous with those of the cranial cavity, ocular hemorrhage does not result from extension of subarachnoid or subdural hemorrhage along these spaces, with rupture through the cribriform plate.[6a,b] However, anatomical studies have shown that retinal and preretinal hemorrhages result from veins acutely distended by the pressure of hemorrhage in the optic nerve sheath. One of the most striking demonstrations of this mechanism was made in a study[6c] on one of the cases used in this series. It cannot be assumed that hemorrhage in the nerve sheath is a direct extension of that in the intracranial intermeningeal spaces. Studies of serial sections of optic nerves in cases of the latter have shown that hemorrhage in the subdural space of the nerve sheath is usually greater than that in the subarachnoid space, even though there was no subdural hemorrhage intracranially.[6d,e] It has been well demonstrated that such nerve-sheath hemorrhages are often patchy, occurring from point to point along the nerve, and that relative amounts of subdural and subarachnoid hemorrhage vary greatly in different sections.[6e] Furthermore, the optic nerve sheath, the only orbital structure continuous with the intracranial meningeal spaces, is not the only orbital structure involved by hemorrhages. They have been found in the orbital fat, muscles, and fascia.[6e] As a result of these findings, various observers are in general agreement that rapidly developing and massive ocular hemorrhages are likely to follow a sudden rise in intracranial pressure. Their observations suggest that the factor responsible for starting the mechanism is sudden pressure on the ophthalmic system of veins as they enter the cavernous sinus. The resulting hemorrhages into orbital structures from acute venous distention intensify the process by exerting more pressure on the peripheral parts of the venous system. In this way, hemorrhage into the optic nerve sheath further occludes already impaired drainage through the central retinal vein and its anastomotic channels, giving rise to acute venous distention and rupture in the retina. It appears from our cases that the presence of subdural hematoma, rather than the subarachnoid hemorrhage, is the main factor that predisposes to formation of large retinal or preretinal hemorrhage. The reason for this may be that the subdural hematoma is confined to a restricted area and that in the case that it results from a ruptured aneurysm, this area will primarily be over the base of the brain, where the maximal pressure effect will be on venous structures of that side. It is interest-

6. (a) Paton, L.: Ocular Symptoms in Subarachnoid Hemorrhage, Tr. Ophth. Soc. U. Kingdom 44:110-124, 1924. (b) Drews, L. C., and Minckler, J.: Massive Bilateral Preretinal Type of Hemorrhage Associated with Subarachnoid Hemorrhage of the Brain, with Case Report and Pathologic Findings, Am. J. Ophth. 27:1-15, 1944. (c) Miller, A. J., and Cuttino, J. T.: On Mechanism of Production of Massive Preretinal Hemorrhage Following Rupture of Congenital Medial-Defect Intracranial Aneurysm, ibid. 31:15-24, 1948. (d) McDonald, A. E.: Ocular Lesions Caused by Intracranial Hemorrhage, Tr. Am. Ophth. Soc. 29:418-432, 1931. (e) Ballantyne, A. J.: The Ocular Manifestations of Spontaneous Subarachnoid Hemorrhage, Brit. J. Ophth. 27:383-414, 1943. (f) Riddoch, G., and Goulden, C.: Relationship Between Subarachnoid and Intraocular Hemorrhage, ibid. 9:209, 1925. (g) Manschot, W. A.: Fundus Oculi in Subarachnoid Hemorrhage, Acta ophth. 22:281-299, 1944.

ing in this regard that the majority of case reports of concurrent subarachnoid and subdural hemorrhage appearing in the literature are those used in illustrating the mechanism of preretinal hemorrhage.[7]

Although the actual point of entry of blood into the subdural space was not identified in any of the cases of ruptured aneurysm, the subdural hematoma appeared to extend from the base in each case. However, widespread extension occurred over the convexities in two cases and over the entire surface of the frontal lobe, including the mesial surface, in another. In exposure of aneurysms at operation, it is not unusual to find arachnoid strongly adherent to the aneurysmal wall. This is probably especially the case when the aneurysm has previously bled. Subsequent rupture of the wall then may occur at, or so close to, such points of arachnoidal attachment that much of the main stream of escaping blood passes through the arachnoid into the subdural space.

SUMMARY AND CONCLUSIONS

In the present series of cases of spontaneous subarachnoid hemorrhage, subdural hemorrhage occurred at the same time in about 4%. The presence or absence of subdural hemorrhage appears to have made no significant difference in prognosis. Concurrent subdural hemorrhage may be suspected in cases in which signs of pressure gradually develop after subarachnoid hemorrhage, especially if unilateral retinal or preretinal hemorrhage is present. In cases of subdural hematoma of obscure origin, a search for intracranial aneurysm is probably indicated.

7. Paton.[6a] Miller and Cuttino.[6c] McDonald.[6d] Ballantyne.[6e] Riddoch and Goulden.[6f]

PAIN FROM DERMAL, PERIOSTEAL, AND FASCIAL ENDINGS AND FROM INFLAMMATION

Electrophysiological Study Employing Differential Nerve Blocks

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THE OBJECTIVE of this investigation was the examination of dermal, subdermal, fascial, and periosteal pain endings accessible from the surface of the body and a comparison of these with the better-known pricking-pain endings located subepithelially. Criteria for comparison were the subjective sensations evoked by comparable stimuli to the skin surface, to deep endings, or to nerves supplying these endings in their course below the skin; the spatial distributions of endings, and the relative thresholds—and therefore the fiber-size groupings—of the nerve fibers mediating the different sensations. Size groups of fibers innervating pain endings were determined by applying differential-pressure and procaine blocks to the peripheral nerves supplying the various sensory endings of the hand, arm, and leg of the human subject. We served as subjects, after considerable training in the discrimination of the effects of painful stimulation of various sorts. Deep endings have been studied recently, by means of mechanical stimulation, by Weddell and Harpman [1] and by Kellgren and McGowan. [2]

After block of delta-fibers, some endings, judged by the sensory quality and latency of their responses to be the endings of C-fibers, can still be stimulated through the skin surface. Along veins and in the periosteum occur groups of endings served partly by delta-fibers and partly by C-fibers, which give a quite different sensory affect from those of pricking pain, even to single-shock stimuli. The sensation is best described as "hurt," and it duplicates the pain from a blow on the shin, or, experimentally, from deep pressure over bone. In muscle fascia comparable endings with similar affect on stimulation were found. A relatively few spots similarly located gave a sharper, pricking pain, more like that from subepithelial endings, also noted by Weddell and Harpman. In immediately subcutaneous tissue, no pain was elicited by needle stabs or by electrical stimuli unless nerve branches were

1. Weddell, G., and Harpman, J. A.: Neurohistological Basis for the Sensation of Pain Provoked from Deep Fascia, Tendon, and Periosteum, J. Neurol., Neurosurg. & Psychiat. 3:319-328, 1940.

2. Kellgren, J. H., and McGowan, A. J.: On the Behavior of Deep and Cutaneous Sensibility During Nerve Blocks, Clin. Sc. 7:1-11, 1948.

approached, as indicated by reference of the sensation to a more distal point. With subcutaneous inflammation, however, this region became irritable to pressure stimulation, and the sensory responses were quite different from those of superficial skin endings.

We are thus dealing with several distinguishable types of sensory mechanisms: sharp, burning pain, probably situated deep in the dermis; deep-pressure pain endings in periosteum and muscle sheaths, and endings in subcutaneous tissue, responding to ordinary stimuli only under conditions of inflammation. It is not certain whether the pain from contraction of ischemic muscle or from deep pressure on muscle bellies, or ache from fatigue, and the like, are to be identified with any of these, such pain arising from within muscle rather than from its sheath, as examined in these studies. However, the similarity of this pain to the pain from inflammation, or that following injection of saline into muscle,[3] suggests that all these endings belong to the class peculiarly sensitive to inflammation.

TECHNIQUE

Stimuli from a medium-sharp instrument or from the point of a No. 24 hypodermic needle were applied to all types of endings studied. Electric stimuli were also applied to all. For the endings and nerves beneath the skin a needle insulated to the point was used. Nerves could be located conveniently by means of electric shocks applied to the skin surface. A 5-mm.-diameter metal disk electrode was employed, with a surface having a curvature of 5-mm. radius. In firm contact with the skin, this served to stimulate touch fibers in superficial nerve branches, below threshold for pricking pain at the site of application. The same electrode was effective in stimulating deeper pain endings along veins and in periosteum over bones near the surface of the body, again below threshold for superficial prick. This was not possible in the cases of endings in muscle fascia.

Differential-pressure block was obtained by means of a blood pressure cuff applied to the upper arm inflated to between 260 and 300 mm. for approximately 45 minutes. At the end of 32 to 37 minutes prick was abolished, but C-fiber pain could still be obtained. C-fiber pain was usually blocked after an additional 10 minutes. Differential block was obtained by injection of 0.5 to 1.0% procaine hydrochloride, from 5 to 15 cc., as needed, along the course of the nerve studied. A relatively large amount of dilute solution gave a more effective differential block than a smaller amount of a more concentrated solution, for the aim was to induce minimal block, or even block of C-fibers without block of delta-fibers. The clearest differentiation was found during recovery from block, and in small branches rather than in main nerve trunks. We were not able to obtain good differential block, for instance, in the ulnar nerve at the elbow but were successful in radial branches at the wrist.

Deep pain was induced by several agents. The most transitory results followed injection of 5% sodium chloride solution. Bee stings, to which one of us is immune through long contact, were applied to the other subject. The most critical results were obtained from the chronic inflammation produced by subcutaneous injection of 0.02 cc. of redistilled turpentine. One nerve was killed by this agent, and one sterile abscess was induced; but in other instances extremely sensitive, indurated areas resulted, 2 to 6 cm. in diameter and persisting from one to two weeks. After more drastic procedures had been tried, the material was injected in the smaller amounts and in aqueous suspension. No pain results immediately from injection of turpentine if the material is placed definitely in the subcutaneous areolar tissue. The resulting inflammation does not then involve the subepithelial endings, whose threshold to mechanical or electrical stimuli remains unaltered. The area injected becomes tender after about two hours and becomes more painful to pressure for a day or two. The reaction then gradually subsides, without permanent after-effects in the more fortunate instances. The indurated area moves freely across the muscle

3. Kellgren, J. H.: Observations on Referred Pain Arising from Muscle, Clin. Sc. **3**:175-190, 1938.

surface, and the pain induced by pinching is definitely superficial to muscle, although the muscle sheaths may be involved also. A margin of nonpainful pitting edema usually surrounds the indurated area.

We employed an electronically operated "thyratron" stimulator delivering shocks at a maximum of 700 volts through an isolation transformer across a resistor of 0.5 meg.[4] Capacity discharges from condensers of 1.0 to 0.02 microfarads (mf.) were available at frequencies up to 200 per second.

RESULTS

Painful Responses to Stimulation of Various Sensory Endings.—When a ball point less than 1 mm. in diameter is applied to the skin surface, a subthreshold single-shock stimulus gives only a sense of contact.[5] Increase of strength induces a feeling of sharpness, as compared with the blunt sensation from the electrode without current, and then prick. On further increase of stimulus the prick becomes distinctly painful, and the sensation persists for an appreciable time after each shock. Sharp prick may be obtained on sensitive pain spots at shock strength too weak to induce touch sensation elsewhere. Effects of successive strong shocks summate at 5 per second to an increasing sensation, and painful pricks fuse to a steady sensation at shock frequencies somewhere above 30 per second, depending on strength. The strong summated effect is a sharp, piercing ache; a weaker summated effect of high-frequency stimulating shocks is a sharp sting, like the bite of a deer fly. These effects can be duplicated by appropriate applications of a sharp point, and loci of mechanically and electrically most sensitive points coincide. Similar pricking pain could also be induced by shallow intradermal injection of small amounts of 5% sodium chloride solution.

Periosteal and other deep endings can also be activated with a similar fine electrode at the skin surface, but only at a strength considerably above the threshold for superficial prick. With an electrode surface of 5-mm. diameter deeper structures can be stimulated alone, especially with shock of long duration. Those sensory spots associated with veins (few have been found along arteries) are punctate, located up to several centimeters apart on the dorsum of the hand, and can be identified by the fact that they move with movement of the skin, in contrast to periosteal endings, the locus of which remains fixed when the skin is moved across them. The periosteal endings over the back of the hand are also punctate, and over the tibia they occur in clusters, at least with respect to the points of highest sensitivity. The sensation induced by single-shock stimulation (except for an occasional point at which an unusually sharp sensation may be obtained, somewhat resembling the pricking pain of the skin) is in general quite different from superficial prick. It is not so abrupt in onset, lacks any feeling of sharp sting, and even to a momentary shock resembles the pain due to pressure from a blunt object. When these endings are strongly and repetitively stimulated, the summation becomes intolerable much more readily than does that from skin endings, and the sensation increases in intensity with temporal summation of stimuli of equal strength. Exactly the same sensation is induced mechanically by pricking periosteal endings with a needle, and if the needle is left in place, the sensation dies away only gradually.

4. Bishop, G. H.: A Simple Electronic Stimulator Suitable for Peripheral Nerve and Skin Sensory Testing, Electroencephalog. & Clin. Neurophysiol. **5**:105-106, 1953.

5. Bishop, G. H.: Responses to Electrical Stimulation of Single Sensory Units of Skin, J. Neurophysiol. **6**:361-382, 1943.

No such endings were found within muscle, where no pain was caused by electrical or mechanical stimulation after the needle penetrated the surface, although injection of 5% sodium chloride solution induced muscle ache. The latter differs in affect, resembling the pain from inflammation rather than that from stimulation of the muscle sheath or that from deep pressure over a bony surface.

It may be noted especially that while the near-threshold effect of stimulation of pricking-pain endings in the skin is not painful, but is merely a sense of sharpness, the deep endings here studied give no such different affect with differences of stimulus strength. The first and only sensation obtained from them is a painful one, which only increases in intensity, without alteration in the character of the sensation.[2] In this respect it resembles pain from electrical stimulation of a tooth cavity or filling. This fact should have a bearing on the theory of pain mechanisms advocated by some psychologists (e. g., Nafe [6]) that pain results from activation of any sensory pathway if stimulated with sufficient intensity. At least here are pathways whose activation induces no conscious sensation other than pain.

Innervation of Deep Pain Endings as Revealed by Differential-Nerve Block.— Impulses giving rise to painful sensation are mediated by two groups of fibers: the delta-, or myelinated, fibers of the A group, with diameters below 6 μ, and the C-, or nonmyelinated fibers. Pain is not induced by stimulation of superficial nerves at any frequency if a strength is used which activates only fibers of larger than delta size [7]; this observation can be established because the thresholds of response of nerve fibers in peripheral nerve trunks to electrical stimulation vary inversely as their diameters.[8] It is known that pressure blocks A-fibers in peripheral nerves before it blocks C-fibers,[9] while procaine blocks C-fibers before A-fibers.[10] The results are cleaner-cut for smaller nerves, in which application both of electric stimuli and of blocking agents can affect all the fibers more uniformly than it can in large trunks with thick sheaths.

In our experience, the differential block of delta- and C-fibers may be made complete and conclusive under the above conditions. The much-debated question whether cuff pressure on a limb blocks by mechanical deformation or by asphyxia is not at issue here, since our requirement is only that for these two groups of fibers the pressure blocks all the delta-fibers for pain while most of the C-group still respond, and that procaine blocks C-fibers while the delta-fibers still respond. The relative rates of depression by anesthetics of large A- and of delta-fibers, also debated, is not an issue, since the presence or absence of superficial pricking pain, easily and accurately recognizable, is to be compared only with other painful

6. Nafe, J. P.: Toward the Quantification of Psychology, Psychol. Rev. **49**:1-18, 1942.

7. Heinbecker, P.; Bishop, G. H., and O'Leary, J. L.: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771-789, 1933.

8. Bishop, G. H., and Heinbecker, P.: Correlation Between Threshold and Conduction Rate in Myelinated Nerve, Proc. Soc. Exper. Biol. & Med. **26**:241-243, 1928.

9. (a) Bishop, G. H.; Heinbecker, P., and O'Leary, J. L.: Function of the Non-Myelinated Fibers of the Dorsal Roots, Am. J. Physiol. **106**:647-669, 1933. (b) Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibers of Slowest Conduction Velocity, ibid. **114**:69-76, 1935.

10. Heinbecker, P.; Bishop, G. H., and O'Leary, J. L.: Analysis of Sensation in Terms of the Nerve Impulse, Arch. Neurol. & Psychiat. **31**:34-53, 1934.

responses, which are equally easily recognizable. The fact is that of the several varieties of pain, two of them, pricking pain and the pain of inflammation, can be differentially blocked by cuff pressure and by procaine; this observation indicates the validity of the technique.

The responses of deep pain endings of muscle fascia, periosteum, and veins were compared with the skin endings for superficial prick in 12 experiments employing cuff pressure, applied to the arm in 11 and to the leg in 1. Branches of the radial, ulnar, forearm cutaneous, and saphenous nerves were stimulated by a needle tip inserted through the skin, during and after pressure block in eight of these experiments. In all cases block of superficial pricking pain was complete after 32 to 37 minutes except in the case of the leg, in which 45 minutes was required. With pressure of 10 to 15 minutes more, deep pain and, in fact, all sensation to mechanical, electrical, thermal, or direct-nerve stimulation had either sharply diminished or disappeared. During the 10 or more minutes after block of pricking pain the following results were consistently obtained.

The sensitivity of pain endings in periosteum, in muscle sheaths, and along veins was considerably reduced *pari passu* with the abolition of superficial prick; but after prick was gone, a higher strength of electrical stimulation, or needle puncture, still elicited severe pain. Sensations of warmth (water at 60 C.) and cold (water at 12 C.) were still distinct. On direct-nerve stimulation, after prick could no longer be obtained, much stronger stimulation induced pain referred largely to deep structures, which was severe with single strong shocks and was summated to overpowering and intolerable deep-pressure ache at low frequencies.[11] In two experiments a distinct referred sensation of warmth was associated. The onset of pain from single shocks to the nerve seemed to be more gradual than before block, and summation to complete fusion, that is, loss of recognition of separate stimuli to the nerve, occurred at a frequency of from 2 to 5 per second. This slow frequency of smooth fusion differentiates the fibers involved from delta-fibers (fusion frequency, 30 per second). Such low-fusion frequency is presumed to be due to slow conduction and correspondingly wide temporal spread in times of central arrival of impulses started with a synchronizing volley in many fibers. The stronger the stimuli after block, the higher was the frequency required for sensory fusion. The increase of fusion frequency with increase of strength of stimulus apparently counteracts the effect of spread of conduction rates within the C-group, and the result confirms the general rule that discrimination is improved with increased intensity of stimulus above threshold.

From these results we infer that the deep endings in muscle fascia, in periosteum, and along veins are all essentially alike both in innervation and in sensory quality of response; that their innervation includes both delta-fibers in the range serving prick sensation in the skin, and C-fibers, and that activation of the latter results in pain of slower onset, but of severer and more penetrating character and of longer aftereffect, as indicated by the slower frequency of smooth summation, than does the activation of delta-fibers. A relatively few deep pain spots give a sharper sensation on mechanical or electrical stimulation, probably because of the delta-fibers con-

11. Pattle, R. E., and Weddell, G.: Observations on Electrical Stimulation of Pain Fibers in an Exposed Human Sensory Nerve, J. Neurophysiol. **11**:93-98, 1948.

tributing to their innervation, for the sharp effect of their stimulation is like that of activation of endings of similar fibers serving superficial prick. When no such sharp sensation is obtained, masking of prick sense by the more overpowering sensation from stimulation of C-endings is inferred.

Procaine block gives results which are not so conclusive as to innervation of these deep endings, for two reasons. First, C-fibers are blocked before delta-fibers; but since all deep endings investigated have both C- and delta-innervation, only a partial loss of deep pain results before prick is blocked, and its degree of loss is difficult to estimate. Second, stimulation of the endings in muscle sheaths is still effective after complete block of superficial skin nerves, indicating that the former are supplied by deep muscle branches. We have not blocked such deep nerves with procaine. However, deep-pressure endings in periosteum over the back of the hand are innervated by branches of the radial nerve. These periosteal endings are rendered ineffective by procaine block at the wrist. This block occurs only at a stage of anesthesia at which pricking pain is also abolished.

Character of Deep Pain Endings Within the Dermis.—The deep endings discussed above are those below the dermis, but within the dermis are endings with certain comparable properties. On differential-pressure blocks these endings proved to be the endings of C-fibers, and results of their activation were compared during block with the sensation induced by activation of the more superficial pricking-pain endings.

As skin prick diminishes under pressure block, the character of sensation changes,[12] and the typical "protopathic," or burning, type of painful response is elicited by either mechanical or electrical stimulation of the skin surface. This burning after-effect, however, is induced only by stronger stimuli than those required for painful response of normal endings before block; if delta-endings were responsible for this changed sensation, such strong stimuli would presumably cause repetitive responses from the endings. In fact, however, the burning pain persists after blocking of pricking pain. As long as this exaggerated sensation under pressure block commences with sharp prick, it may be inferred that delta-fibers remain, and this inference is confirmed by production of prick by nerve stimulation at the strength inducing prick before block. It has been noted above that with C-fiber stimulation after block of delta-fibers, one obtains a severe ache, poorly defined, and referred to deep endings more emphatically than to superficial skin endings.

With direct skin stimulation after delta-fiber block the situation is clearer; there is an easily detected latency of at least half a second after strong electric shocks. In addition, there is a much more pronounced effect of temporal and spatial summation, either in response to repetitive electric shocks or to drawing a sharp point across the skin, than to a single prick stimulus. Localization of the stimulus is poor, although roughly present, and the same stimulation to the two arms, one of which is blocked to the elimination of delta-fiber pain, gives the effect on the latter of much greater intensity of pain, as well as greater persistence and a different quality, the

12. (*a*) Lewis, T., and Pochin, E. E.: Effects of Asphyxia and Pressure on Sensory Nerves of Man, Clin. Sc. **3**:141-155, 1938. (*b*) Weddell, G.; Sinclair, D. C., and Feindel, W. H.: An Anatomical Basis for Alterations in Quality of Pain Sensibility, J. Neurophysiol. **11**:99-109, 1948.

quality being obviously that reported by patients with nerve lesions as burning pain. The mere elimination of pricking pain seems to result in a release of central affect of C-fiber activations, and this implies a normal masking effect upon these responses by the activity of the pricking-pain mechanism.

Block of an order the reverse of pressure block, which could be induced with procaine, proved effective in studying these deep dermal endings. In all the experiments employing procaine cited in the next section there occurred a stage of recovery of pricking pain at which C-fiber pain must still have been blocked. In no case was an exaggeration of painful response noted as above normal, assignable to overaction in a reduced pattern of peripheral representation. This agrees with the findings of Langley[13] and Trotter and Davies[14] that cocaine block does not result in hyperalgesia, such as that found after nerve section.

We performed three experiments specifically to check the results of differential block of these endings. Thresholds for prick were recorded before block, and reports of the quality of sensation elicited by single and repetitive stimuli at several strengths above threshold were obtained. In two experiments on normal arm skin, only a diminution of prick, a dulling of its quality, and a progressive raising of threshold occurred during anesthesia induced with 0.5% procaine hydrochloride, and the reverse changes occurred during recovery. That is, with all C-fibers blocked and a reduction in the number of delta-fibers still active, there was still no hyperalgesia resulting from the stimulation of the reduced number of delta-endings whose fibers remained unblocked, at any strength or frequency of stimulation.

In a third experiment, a member of the laboratory (M. H. C.) was available, also trained in sensory examination, who three and a half months before had received an accidental cut across the dorsal surface of the fifth finger close to the proximal margin of the proximal phalanx. The typical hyperalgesia, including the burning-pain after-effect of electrical or mechanical stimulation, was obtained over the dorsum of the proximal phalanx, and, to a less degree, over the middle phalanx. During block by procaine of the dorsal branch of the ulnar nerve at the wrist, there occurred a progressive, and finally complete, loss of the disagreeable character of response over the proximal phalanx, at stimulus strengths up to 20 times the normal threshold for prick. A few, and diminishing, number of prick spots remained, although threshold to prick sensation materially increased during block. The report was that the sensation to adequate stimuli became more like normal prick with deeper anesthesia, in spite of the increased strength of stimulus required. The remainder of a few spots giving prick after maximal block was presumably assignable to overlap from the volar branch of the digital ulnar distribution. (The dorsal branch innervates chiefly the proximal phalanx of the fifth finger, the remainder of the dorsum of the finger being supplied partially by the volar nerves.)

Differential Block of Subcutaneous Inflammatory Pain.—In three satisfactory experiments, 0.02 cc. of turpentine injected subcutaneously caused deep inflamma-

13. Langley, J. N.: Effect on Nail Growth and Sensation of Section of a Cutaneous Digital Nerve, and Effect on Sensation of Cocainizing a Cutaneous Nerve of the Foot, J. Physiol. **36**:45P-46P, 1907.

14. Trotter, W., and Davies, H. M.: Experimental Studies in the Innervation of the Skin, J. Physiol. **38**:134-246, 1909.

tion without altering the threshold or the quality of response to superficial prick stimulation. In two of these experiments the underlying muscle sheaths were slightly involved, to the degree of remaining tender during contraction of the muscles even after complete procaine block of nerves to overlying skin. Before block a number of pricking-pain spots were marked and their thresholds to electric stimulation determined.

Superficial nerves supplying these lesions were completely blocked by procaine nine times, each time ache and tenderness to pressure being effectively removed from the subcutaneous indurated mass. In all but one trial block was too rapidly induced to be followed accurately; it was usually complete in two to five minutes. In the one case inflammatory pain was abolished 30 seconds before loss of pricking pain was complete. In all cases on the nerve coming out of block, good differentiation was obtained. Prick returned after 20 to 40 minutes. Inflammatory pain was completely absent for from 13 to 40 minutes after the first return of prick, and in three trials it was absent for 20 minutes after prick sensation was judged normal.

In the case of one of these lesions, on the forearm, the convenient blocking of a single nerve branch split the indurated region, with sparing of the lateral one-fourth of the painful area. Of the 10 pricking-pain spots marked over the indurated area, all but 1 were blocked, this one lying over the unblocked region of the painful area. The unblocked portion offered a convenient standard of comparison for the differential reappearance of two types of pain, and its presence indicates that nerve branches supplying subcutaneous tissue distribute fibers to the immediately overlying skin, as might, in fact, be expected.

In all nine trials it was thus demonstrated that no pricking-pain fibers were involved in the transmission of painful sensations from subcutaneous inflammation.

In addition to lesions from turpentine, one of us was subjected to three bee stings, two on the hypothenar eminence of the hand and one in the saphenous distribution of the leg. All gave a good inflammatory response, marked tenderness and pain to pressure, and only slight ache, without pressure. In one instance a nerve was blocked with procaine; in two, cuff pressure was applied. After procaine block, slight prick had returned after 25 minutes; prick sense was normal after 70 minutes, and a painful response to pressure was not obtained for 20 minutes more, the last returning to normal over the next 40 minutes. In the two tests with cuff pressure, prick sensation was blocked in about 35 minutes, leaving pain to pressure only slightly diminished five minutes later. In one of these experiments deep pressure spots had been marked in normal areas over the back of the hand for comparison with the inflamed area, and their sensitivity had been found to be definitely diminished, but had not been abolished at the end of the test. The cutaneous nerve supplying the area of these pain spots was then stimulated by a subcutaneously placed needle point, and deep pain was elicited by strong stimulation after block of skin prick. While some of the fibers serving these deep pain spots had previously been found to fall in the range of delta-fibers, the remainder proved to have the same resistance to pressure block as did the subcutaneously distributed fibers responding to inflammation.

Pain from Injection of Sodium Chloride Solution and from Previous Injury.— During the course of these procedures a number of observations were made on the results of injecting 5% sodium chloride solution into the interior of muscles, into

subcutaneous tissue, and into the inflamed area resulting from bee sting. Care was taken not to place the saline solution in contact with muscle sheaths or periosteal surfaces. The resulting pain, except for a somewhat more acute quality, resembled the pain resulting from pressure on an inflamed area rather than that from deep pressure over periosteal endings. The results on this type of pain of blocking by cuff pressure or by procaine corresponded to the results on inflammatory pain, and it may be inferred that in the regions injected, predominant C-fiber pain was aroused, and from the same endings as are there sensitized under inflammation. This does not mean that such injection does not elicit pain in regions where delta-endings are present; rather, it confirms the conclusion that in these regions of muscular and subcutaneous tissue delta-endings are functionally scarce or absent.

Stimulation of the inflamed area of subcutaneous tissue resulting from a bee sting with strong shocks was tried in one instance. This did not result in any exaggeration of pain, such as that induced by normal skin stimulation with the nerve under pressure block; from this we might infer that the endings reached were not concentrated enough to permit the spatial summation necessary for arousal of inflammatory pain.

Incidental observations were made on the tenderness from a healing interphalangeal fracture of the fourth finger of one subject. Tenderness on passive movement behaved in cuff-pressure experiments like the inflammatory pain of bee sting. While we cannot say in this case that no delta-fibers were involved in this tenderness, we believe it safe to conclude that the pain was chiefly assignable to activation of C-fibers, and that the condition of increased irritability was presumably of the character of inflammation.

COMMENT

In this study emphasis has been placed on correlation of the type and distribution of pain endings with the fiber sizes in peripheral nerves supplying them. For pricking-pain endings at least, the terminal segments, whose fibers are myelinated more proximally, lose their sheaths as they approach the skin, and probably all sensory terminals are nonmyelinated. Nothing can be concluded, therefore, about the electrical or other sensitivity of peripheral endings on the basis of their diameters; the endings are selectively activated by reason of factors other than diameter. In the case of pain, the quality of sensation does not correlate entirely with the diameters of fibers in the nerve trunk, deep-pressure pain being carried in part over similar fibers to fibers mediating superficial pricking pain.

On the other hand, at a cross section of peripheral nerve, all functions transmitted must be represented by patterns of impulses in fibers, and both the character of the impulse patterns and the fiber properties can be specified under suitable experimental conditions and inferred in less accessible situations. If the properties of the processes which result in sensation are correlated with the impulses passing through groups of peripheral nerve fibers, it becomes possible not only to compare one set of properties with another in common terms, but to apply a large amount of physiologic information to the characterization of the sensory process. Further, in the electrical stimulation of such nerve cross sections, the frequency and intensity of applied stimuli can often be so selected as to imitate the normal effects of stimulation of those endings, and thus assist in the interpretation of the action of the

endings themselves. Information concerning fiber groups supplying sensory endings may then be employed in the analysis of the sensory process in general.

To put this work in its appropriate perspective, the following brief summary of the pertinent properties and functional connotations of nerve-fiber groups is presented. A detailed discussion of certain points still in question is not necessary here, and the selection made represents our own opinions. There are in peripheral nerves three main groups of fibers, A, B, and C. The C-, or nonmyelinated, group contains both sensory and motor fibers, the latter being autonomic in function. The sensory C-fibers have been assumed to include fibers for both pain and temperature sense. The B-fibers are entirely (motor) preganglionic autonomic fibers and are thinly myelinated. In the A-, or myelinated, group can be recognized in some nerves (to skin and muscle) four subgroups. The first, containing the largest fibers, which give rise on conduction to the alpha wave, includes fibers for proprioception and motor fibers to striated muscle. This component is absent or small in cutaneous nerves. The second, or beta-subgroup includes tactile sensory fibers innervating hair follicles and is present in cutaneous and mixed nerves. Some motor fibers to muscle overlap this range. The third, or gamma-group, in sensory branches, is not known to be functionally different from the beta-group, but probably include other fibers for touch sensation. In muscle nerves the range of motor fibers overlaps this also. The fourth, or delta-group occurs in skin nerves, serving pain and temperature sense (and probably including more touch fibers). In muscle nerves a group of smaller motor fibers of $4-\mu$ diameter innervates muscle spindles. Fibers serving pain sense from muscle are included in the delta range, although no prominent delta wave is observed, and the same is true of many nerves other than those going specifically to muscle.

These groups are recognizable after conduction from a volley stimulus because of differences in conduction rate—the smaller the fiber in general the slower its rate of conduction. There are not absolute intervals between most of these successive groups, but the pattern consists of alternate maxima and minima, in a more or less continuous spectrum of size and conduction rate. The delta elevation is particularly discrete in skin nerves, and this fact has facilitated study of delta-fiber pain.

Many properties of nerve fibers besides conduction rate can be correlated with diameter, and thus indirectly with functional relations; but in the present context the three significant correlations are as follows: The larger the fiber, the lower is its electrical threshold, the less is the duration of pressure required for block of conduction, and the greater is the resistance to block by local anesthetic. Regardless of the precision with which closely adjacent groups can be differentiated by these means, the differences in these respects between delta- and C-fiber groups are sufficient completely to separate them in small nerve branches by blocking procedures gradual enough to approach equilibrium states. Too rapid block by pressure, too high a concentration of anesthetic, or thick nerve sheaths, resulting in gradients of effects across the nerve diameter, lead to equivocal results.

We wish to emphasize that to make the results of any differential procedure conclusive it is necessary to eliminate one factor completely while leaving a significant fraction of the other intact; that is, the overlap of the two factors should be minimal, if not ideally zero. The statistical estimation of loss of function to arbitrary end-

points, such as a certain reduction in number of positive reports during block,[15] must be equivocal for a categorical determination of what is blocked. The delta- and C-fiber elevations in the nerves of unanesthetized dogs can be effectively separated by tourniquet pressure as checked by oscillographic recording from the intact nerve proximal to the block.[9] The delta-wave completely disappears from the record when little change in the C-wave has occurred, and pain is still induced by C-fiber stimulation when no evidence of pain results from any stimulation of less strength, stimulation which checks the effectively complete block of delta-pain fibers.[16]

In the human subject it is not possible to obtain the nerve record against which the subjective sensation could be checked, but it is possible to correlate unequivocally superficial pricking pain with the stimulation of delta-fibers on the basis of the known relative thresholds of delta- and beta (touch)-fibers.[7] The fact that inflammatory pain can be completely abolished by procaine block of the nerve trunk, still leaving pricking pain intact, gives one the opposite correlation. This justifies the conclusion that deep-pressure pain, in contrast to subcutaneous inflammatory pain, is supplied by both C- and delta-fibers, in spite of the difficulty of estimating how much of the sensory effect is due each, and in spite of the more confusing fact that in the case of deep pressure, the sensory quality of the responses of the two sets of endings is not significantly different. In short, the variety of subjective painful sensations so complicates the issue that only by using all the criteria available can subjective sensation and the peripheral mechanism of reception and conduction be adequately related.

It has been stated above that the pain of pressure is remarkably increased after inflammation confined to tissue which is specifically subcutaneous. This does not mean that no pressure pain from normal subcutaneous tissue can be obtained, or that inflammation at pain endings elsewhere does not increase their sensitivity, or that only C-fiber endings are made more sensitive by inflammation. The point is that we have here isolated a region where only C-pain endings respond and that they prove to be insensitive to ordinary prick stimuli. Similarly, Bull and Lennard-Jones [17] noted that pain was elicited from the subcutaneous tissue after full-thickness burns only when inflammation was present. By pinching a fold of loose skin severely between the fingers, taking care not to crease the skin sharply in the process, one can, in fact, obtain dull pain somewhat similar in quality to inflammatory pain, and quite different from superficial pricking pain. If the pressure is transferred to the apex of the fold so as to crease the skin acutely, the sensation changes to sharp superficial pricking pain. The relative degree of pressures required for stimulation of pain in normal and in inflammatory subcutaneous tissue is striking, and is sufficient to indicate that the usual, normal pain sensation from pressure or

15. Sinclair, D. C.: Observations on Sensory Paralysis Produced by Compression of a Human Limb, J. Neurophysiol. **11**:75-92, 1948. Sinclair, D. C., and Hinshaw, J. R.: Sensory Changes in Procaine Nerve Block, Brain **73**:224-243, 1950; A Comparison of the Sensory Dissociation Produced by Procaine and by Limb Compression, ibid. **73**:480-498, 1950; Sensory Changes in Nerve Blocks Induced by Cooling, ibid. **74**:318-335, 1951.

16. Clark, Hughes, and Gasser.[9b] Bishop, G. H., and Heinbecker, P.: Afferent Function of Non-Myelinated or C Fibers, Am. J. Physiol. **114**:179-193, 1935.

17. Bull, J. P., and Lennard-Jones, J. E.: Impairment of Sensation in Burns and Its Clinical Application as a Test of the Depth of Skin Loss, Clin. Sc. **8**:155-169, 1949.

impact is chiefly due to fascial and periosteal endings below the subcutaneous tissue.[2] It justifies the inference that the type of endings found here, and presumably present elsewhere in the body where inflammation results in pain not otherwise encountered, are particularly adapted to record, not primarily the acute effects of injury, but the secondary effects of tissue damage. That other endings are also made more sensitive by inflammation, however, is obvious from casual experience with superficial scratches, infections, bruises, etc.

If subcutaneous endings or, equally, endings within muscle are normally sensitive to pressure, in whatever degree, the question is why deep prick or insertion of a hypodermic needle causes no pain after penetration of the superficial skin or muscle fascia; injection of sodium chloride solution from the same needle tip is sharply effective. Yet an inflamed area of subcutaneous tissue is not unusually sensitive to needle prick or electric shock, although involvement of the dermis by the inflammation, as in the usual infection, greatly enhances the sensitivity of intra-dermal endings. The most obvious explanation, by no means novel here, is that some degree of summation is required to render stimulation of pain endings effective. The discrete loci of pain found in the periosteum and along veins appear to be punctate, an observation which, however, may mean only that the most sensitive loci represent concentrations of endings, like those of pain spots in the skin, permitting spatial summation to even a momentary stimulus. To a sufficient pressure stimulus any point over bone is painfully sensitive. Temporal plus spatial summation is the obvious result of inflammation or injection of sodium chloride, and even in the case of superficial prick spots, summation (either temporal or spatial) can be shown to be the necessary requirement for painful experience.[5] Even in the skin, threshold stimulation of a spot causes no pain, nor does stimulation of a few potential "pain" fibers in a nerve by a single shock. It is, in fact, questionable whether one impulse in one pricking-pain fiber is perceptible at all. It might be inferred, then, that endings in subcutaneous tissue and in other situations with similar pain characteristics differ from the more specifically and acutely excitable pain spots by reason, among others, of their less concentrated or less punctate pattern of distribution.

The remarkable enhancement of the sensory response to skin stimulation occurring after block of pricking-pain fibers throws light on several aspects of sensory behavior. First, it has repeatedly been inferred [18] that the completeness of the afferent pattern of excitation is a factor in central response and that after partial denervation of an area the stimulation of the remaining pain endings results in an abnormally intense affect, having the character of burning pain. This relation of partial loss of endings to hyperalgesia has generally applied, specifically or by implication, to pricking-pain endings of the subepithelial network. It can now be inferred that this theory applies equally to the nonmyelinated fibers which end deeper in the dermis,[19] and, more specifically, that it applies to the effect of loss of pricking-pain endings on the sensation induced at C-fiber endings. This relationship points, in fact, to a masking or to a suppression of response of C-fiber endings in normal experience due to the presence of the more easily excitable delta-fiber pain responses.

18. (a) Tower, S. S.: Pain: Definition and Properties of the Unit for Sensory Perception, A. Res. Nerv. & Ment. Dis., Proc. **23**:16-43, 1942. (b) Bishop, G. H.: Neural Mechanisms of Cutaneous Sense, Physiol. Rev. **26**:77-102, 1946. (c) Weddell, Sinclair, and Feindel.[12b]

19. Kuntz, A., and Hamilton, J. W.: Afferent Innervation of the Skin, Anat. Rec. **71**:387-400, 1938. Weddell, G.: The Anatomy of Cutaneous Sensibility, Brit. Bull. **3**:167-172, 1945.

We would agree with Wortis and associates,[20] Bigelow and associates,[21] and Kendall [22] that in neurological conditions of hyperalgesia involving lesions of the conducting system anywhere below the sensorium, the overaction is probably due not merely to numerical loss of representation of endings, but, rather, to a more specific release of C-fiber sensory affect. These patients typically report a dulling of sharpness of prick, followed by a burning after-effect, which is rather exactly duplicated in our own experience during the period when we know that delta-fibers are being progressively blocked and when C-fibers have not yet been significantly affected. Whether the hyperalgesia is entirely assignable to release of C-fiber pain responses will require further work to determine, but this interpretation is consistent with the results of procaine block to the one hyperalgesic lesion recorded above.

This condition of reduction of prick with burning-pain overaction to noxious stimuli reaches its extreme in tabetic patients.[23] We have examined two such patients before and during the 45-minute application of cuff pressure of 290 mm. above the knee. Each showed severe loss of pricking pain before block, but still some few points where sharp prick was reported. One had prominent symptomatic plantar dysesthesia. After 35 minutes of pressure application, no sharp-pricking pain spots remained; electrical or mechanical stimulation elicited a report of delayed, mild, and poorly localized burning pain. With a stronger stimulus, or if the stimulating point was moved across the skin surface, the patients reported a scratch with a burning-pain after-effect. Burning pain could readily be elicited in the blocked or in the unblocked leg with strong electrical stimulation by the 5-mm. electrode, without pricking pain. The delay of perception of pain to plantar scratch or electrical stimulus was over one second in both legs, and the patients could not distinguish qualitatively between the sensations from the two legs, although the discomfort from the blocked leg was often severer. As nearly as we can identify the patients' reports with our own experience after block, the sensation was in all essentials the same, and no pathological process other than that involving loss of myelinated pain-fiber conduction is demanded to account for the character of the painful responses of these patients. These conclusions are provisional, pending a more extensive study of this condition.

A second aspect of the enhancement noted involves the question of delayed pain. It is obvious that block or pathological suppression of delta-pain-fiber responses releases C-fiber-response perception in an otherwise normal subject; that quite superficial skin stimulation, with a threshold, to be sure, somewhat higher than that of pricking pain, is then an adequate stimulus; that such pain may arise from endings in the dermis, and that stimulation of deeper endings is not required. The sensory responses then obtained are characterized by a long latency and a greatly increased intensity as compared with the results of the same stimulation in the

20. Wortis, H.; Stein, M. H., and Joliffe, N.: Fiber Dissociation in Peripheral Neuropathy, Arch. Int. Med. **69**:222-237, 1942.

21. Bigelow, N.; Harrison, I.; Goodell, H., and Wolff, H. G.: Studies on Pain: Quantitative Measurements of 2 Pain Sensations of Skin with Reference to the Nature of "Hyperalgesia of Peripheral Neuritis," J. Clin. Invest. **24**:503-512, 1945.

22. Kendall, D.: Some Observations on Central Pain, Brain **62**:253-273, 1939.

23. Pochin, E. E.: Delay of Pain Perception in Tabes Dorsalis, Clin. Sc. **3**:191-196, 1938.

intact subject. These characteristics correspond in all respects to those of delayed or second pain, generally assigned to C-fiber activation,[24] although some investigators have not accepted this thesis.[25] One of us (G. H. B.)[15b] has previously expressed doubt that C-fiber pain could be aroused from intradermal endings, and the inference was made that the phenomenon of delayed pain, elicited as it is in the normal only by rather violent stimuli, might be explained as a complex summation of responses of touch, pressure, and prick endings, plus a persistence due to the damaging effect of the stimulus. These doubts were aroused by the inability to induce two pains by electrical stimuli, and, in fact, by any stimuli whose effects could be reasonably referred to stimulation of dermis only. Such doubts are now resolved, and the failure of brief stimuli to give rise to a sensation of delayed pain can be assigned to the masking effect of pricking-pain stimulation.

As a check on this point, eight normal, unprejudiced subjects were tested with heat, electrical, or brief mechanical stimuli, and only three thought they could recognize a second pain response. The contrast between these results and those after block in the normal or in the tabetic subject is unmistakable.

Finally, the differential separation of the two sensations assignable to two classes of nerve fibers puts the work of Head and his colleagues [26] in a new light. It appears that these investigators were correct in their conclusions, though for reasons which were not altogether adequate. We can find no fault with Trotter and Davies'[14] criticisms of Head's reasoning, on the basis of their own excellent analysis of the course of sensory change after nerve section. However, one of their chief objections to Head's argument seems to be unjustified. They stated (page 208):

We are no longer compelled to ascribe it [the hyperalgesia] to a mechanism so unassimilable with the rest of our knowledge . . . that increase in sensitiveness to one stimulus is produced by a loss of sensitiveness to a totally different one.

At the time of their writing the existence of two quite different groups of pain fibers had only been inferred by Head, and had not been demonstrated, and the effects of their differential and combined stimulation now prove to be exactly those which Head inferred, and to which Trotter and Davies strenuously objected. The other points of criticism of Head's findings, especially Trotter and Davies' careful analysis of the course of hyperalgesia during the interval between nerve section and final recovery to normal, will require further work to be dealt with adequately.

SUMMARY

Pain induced in human subjects by stimulation of various endings in skin and subdermal tissues has been studied by electrical and mechanical stimulation. Also included was the pain from subcutaneous inflammation due to turpentine injection and bee sting. In addition, nerve branches beneath the skin were stimulated at controlled intensities to induce pain. The subjective sensations were compared with those of pricking pain as a standard, the latter being known to be due to activation of endings of delta-, or small myelinated, nerve fibers.

24. Lewis, T., and Pochin, E. E.: Double Pain Response of the Human Skin to a Single Stimulus, Clin. Sc. **3**:67-76, 1937.

25. Wollard, H. H.; Weddell, G., and Harpman, J. A.: Observations on the Neurohistological Basis of Cutaneous Pain, J. Anat. **74**:413-440, 1940.

26. Head, H.; Rivers, W. H. R., and Sherren, J.: Afferent Nervous System from a New Aspect, Brain **28**:99-115, 1905.

Pain was also induced by stimulation of fibers or of their endings of the C-, or nonmyelinated, group. The two groups of fibers in peripheral nerves of the arm and leg were differentially blocked, the delta-fibers being blocked by cuff pressure, leaving C-fibers only conducting, and the C-fibers being blocked by procaine, leaving delta-fibers only conducting.

Periosteal endings, endings in muscle sheaths, and those along veins were found to be supplied by fibers of both types. Pricking-pain endings in the skin appeared to be confined to the subepithelial network, except that a delta-fiber component to certain deep sensory spots probably contributes a sharpness to the more penetrating ache which characterizes the result of C-fiber stimulation. C-fiber endings, deeper in the dermis proper than the endings for pricking pain, gave on stimulation after block of prick sensation the delayed, persisting, and burning type of pain characteristic of the results of partial nerve lesions and of tabes.

Inflammatory subcutaneous pain is assignable almost entirely to activation of C-fiber endings, which seem to be specifically sensitized by inflammation; pinching or puncturing normal subcutaneous tissue was relatively painless. Injection of 5% sodium chloride solution also excited these endings effectively, as it did also intramuscular endings. It is inferred that such endings are distributed generally in the body and serve the function of registering the sequelae of tissue damage, rather than the immediately injurious incident itself.

Many deep endings are punctately distributed, although between these most sensitive spots pain can still be elicited by stronger stimulation. Such sensory spots probably consist, as do those for pricking pain in the superficial skin, of localized concentrations of endings. The subcutaneous endings responding to inflammation are not punctately arranged.

After block of delta fibers by pressure, the pain from stimulation of C-fiber endings was greatly exacerbated after a given strength of stimulus. This points to a remarkable masking or suppression of the C-fiber sensory affect by delta-fiber activation under normal conditions. No such overaction of delta-fibers was obtained, even when part of them were blocked, when C-fibers had been blocked previously by procaine. This unmasking of C-fiber pain by loss of delta innervation is sufficiently pronounced to account for the burning after-effect of stimulation following partial nerve damage or in tabes. These phenomena appear to justify some of the conclusions of Head as to two varieties of pain fibers and their differential action following nerve section in the region of partial loss.

The results of C-fiber activation show the following differences from the results of delta-fiber activation: longer latency; penetrating and burning ache, as compared with sharp prick or sting; summation to a continuous sensation at a frequency of 2 to 5 per second, as compared with the frequency of 30 per second required for pricking pain, and overaction to effective stimulation in the absence of delta activity. The thresholds of the endings of C-fibers are probably higher than those of delta-fibers under comparable conditions, but the discrepancy is far less than is the difference of thresholds of delta- and C-fibers in nerve trunks.

AN EXTRALEMNISCAL SENSORY SYSTEM IN THE BRAIN

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IN RECENT years it has become apparent that afferent impulses may reach the cortex by routes distinct from those involving transmission along the classic sensory pathways to the primary receptive areas. In 1936, Derbyshire, Rempel, Forbes, and Lambert [1] called attention to impulses evoked by sciatic stimulation which it was possible to record in areas remote from the sensorimotor strip and which had latencies much longer than did potentials confined to this region. These longer-latency potentials were called the "secondary" responses by Forbes and Morison,[2] as distinct from the "primary" responses, which had long been well known. Characteristic differences between these two distinct sensory systems aside from projection distribution and latency were elaborated by Dempsey, Morison, and Morison,[3] who presented evidence suggesting that the pathway for the "secondary" response might be the medial division of the medial lemniscus and that it might course more centrally before becoming widely dispersed throughout the cortex.

While no definite function was imputed to this "secondary" sensory system, features concerning its course and distribution closely resembled those more recently shown to subserve the arousal responses to afferent stimulation. Thus, it has been demonstrated that sensory impulses reach the central cephalic brain stem presumably through collateral fibers from the well-known lateral ascending pathways [4] and that

1. Derbyshire, A. J.; Rempel, B.; Forbes, A., and Lambert, E. F.: Effects of Anesthetics on Action Potentials in the Cerebral Cortex of the Cat, Am. J. Physiol. 116:557-596 (Aug.) 1936.

2. Forbes, A., and Morison, B. R.: Cortical Response to Sensory Stimulation Under Deep Barbiturate Narcosis, J. Neurophysiol. 2:112-128 (March) 1939.

3. Dempsey, E. W.; Morison, R. S., and Morison, B. R.: Some Afferent Diencephalic Pathways Related to Cortical Potentials in the Cat, Am. J. Physiol. 131:718-731 (Jan.) 1941.

4. (a) Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Collateral Afferent Excitation of Reticular Formation of Brain Stem, J. Neurophysiol. 14:479-496 (Nov.) 1951. (b) French, J. D.; von Amerongen, F. K., and Magoun, H. W.: Activating System in the Brain Stem of the Monkey, A. M. A. Arch. Neurol. & Psychiat. 68:577-590 (Nov.) 1952.

potentials evoked by stimulation of this central region can be recorded diffusely over the cortical mantle.[5] Since excitation of this area by repetitive stimuli delivered directly to it or to peripheral sensory receptors results in electrocortical desynchronization and behavioral arousal of a sleeping animal, the area has been called the reticular activating system.[6]

These recent observations have all been obtained with ink-written electroencephalographic recording. The present study has made use of the cathode-ray oscilloscope to analyze more fully temporal and other features of ascending conduction in the central reticular formation of the brain stem, as compared with those in classic sensory paths.

METHODS

Experiments were performed on 12 monkeys, the initial exposure only being made with the animal under ether anesthesia plus the application of procaine to exposure margins and pressure areas. Subsequent observations were made after immobilization of the animal with decamethonium chloride (syncurine*), respiration being maintained by artificial means through a tracheal cannula.

Single-shock condenser-discharge stimuli (5 volts, 1 msec.) were delivered from a Goodwin stimulator to the central end of the divided sciatic nerve. Auditory stimuli of 1-msec. duration were delivered from a pulse generator and amplifier directly to the external ear through a hollow ear lug and rubber tube. Potentials were recorded from primary receptive areas (the superior temporal gyrus was exposed by subpial resection of the parietal operculum) and from various associational areas of the cortex through silver ball electrodes. Subcortical potentials were recorded by bipolar nichrome wire electrodes oriented through a craniotomy opening by means of the Horsley-Clarke stereotaxic instrument. Records were made simultaneously on a Grass electroencephalogram and ink-writer and on a double- or single-beam cathode-ray oscilloscope. In obtaining the latter records, the beam was photographed with a Fairchild camera, employing either a triggered sweep (3- to 30-msec. per centimeter sweep speed) or a running film (4 to 20 in. a second). At the completion of each procedure electrode placements were verified anatomically.

RESULTS

The present study confirms earlier findings [4b] in showing that upon peripheral afferent stimulation ascending impulses are conveyed to the cortex both in classic sensory paths and through the length of the more central portion of the brain stem (Figs. 1 and 2). Contrasting features were exhibited by the discharge evoked in these dual routes for corticipetal conduction.

The potentials recorded in lateral sensory paths had brief latencies and steep-rising phases, so as to be spike-like in configuration. Thus, on sciatic stimulation, impulses arrived in the medial lemniscus at the midbrain level 6 to 9 msec. (Figs. 1 and 2C) and in the postcentral gyrus 10 to 12 msec. (Figs. 1 and 2D) after the stimulus. Auditory stimuli evoked potentials which were somewhat slower, reaching the lateral lemniscus in 9 to 11 msec. and the auditory cortex in 13 to 17 msec. (Fig. 2 C¹ and D¹).

In contrast, discharges evoked by the same afferent stimuli in more central locations in the brain stem had a distinctly longer latency and more sloping rise

5. Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Ascending Conduction in the Reticular Activating System with Special Reference to the Diencephalon, J. Neurophysiol. **14**:461-477 (Nov.) 1951.

6. (a) French, von Amerongen, and Magoun.[4b] (b) Moruzzi, S., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949.

and fall, so as to be wave-like in configuration. Thus, sciatic and auditory potentials reached the pontile and mesencephalic tegmentum and the midline portion of the thalamus in 13 to 23 msec. (Figs. 1 and 2A and A^1, B and B^1), an increment of 7 to 14 msec. over lemniscal times, and took correspondingly longer intervals to arrive at the frontal associational cortex (Figs. 1 and 2 E, E^1). In the medial brain stem, the peak of such evoked discharge was recorded 20 to 30 msec. after the stimulus (Figs. 2A, A^1 and B, B^1), as compared with 15 to 16 msec. in the medial or lateral lemniscus (Fig. 2C, C^1). Both the long latency and the prolonged maintenance of activity evoked in the medial brain stem by afferent stimulation indicate that a number of relays must be involved in ascending transmission through this
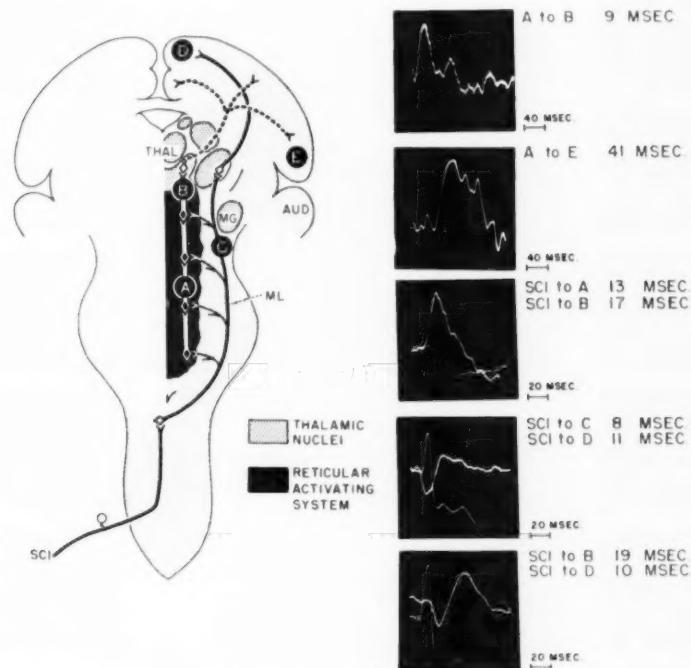

Fig. 1.—Conduction time of evoked potentials to the brain stem and cortex. The left-hand figure illustrates recording points of evoked potentials on stimulation of the sciatic nerve. The photographs of the oscilloscope recordings on the right side show relative latencies at the appropriate points lettered. The upper two records show evoked potentials resulting from stimulation of the caudal reticular formation as recorded in the medial thalamus and the frontal association cortex.

region. This relatively slow propagation of impulses in the medial brain stem is further indicated by the observation that transmission from central bulb to medial thalamus, a distance of 15 mm., required 5 to 9 msec. (Figs. 7 and 8).

The distribution of sites from which such central activity has been recorded did not follow the course of any recognized long ascending pathway. The area concerned is seen in Figure 3 to include the pontile and mesencephalic tegmentum and the

midline portion of the diencephalon. There was some suggestion of grouping of active points into ventrally and dorsally situated portions of the area, although potentials were evoked in the entire region. Caudally, they appeared in the reticular formation and periaqueductal gray matter (Fig. 3D, E, and F). Within the diencephalon, potentials were recorded in the subthalamus and hypothalamus, adjacent to the third ventricle (Fig. 3B and C). In the thalamus only the centrum medianum (Fig. 3D) and nucleus centralis and nucleus centralis lateralis (Fig. 3C) were implicated. These medial connections thus appeared to constitute a diffuse
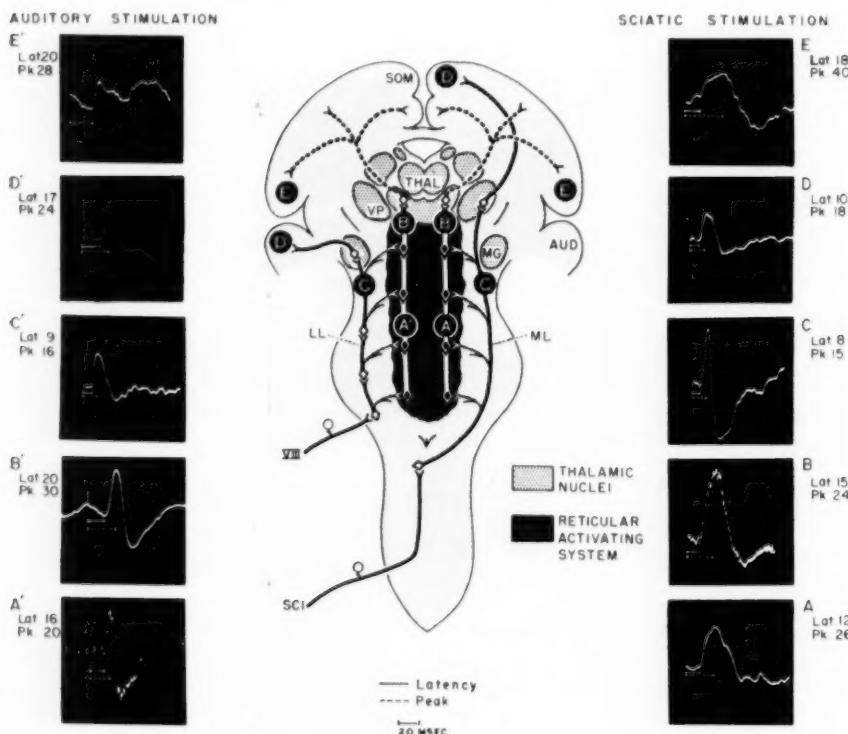

Fig. 2.—Latencies of potentials in brain stem and cortex evoked by sciatic and auditory stimulation. The central diagram illustrates recording points for potentials evoked from sciatic stimulation on the right side and potentials evoked from auditory stimulation on the left side. Photographs of oscilloscopic records of such potentials at designated points are correspondingly labeled. Note short latencies in lateral sensory pathways (C and C') and in primary sensory receptive area of cortex (D and D') and longer latencies in reticular activating system (A and A'), medial thalamus (B and B'), and association cortex (E and E'). SCI indicates sciatic nerve; LL, lateral lemniscus; ML, medial lemniscus; MG, medial geniculate body; VP, nucleus ventralis posterior of thalamus; THAL, thalamus; SOM, somatic primary receptive area of cortex; AUD, auditory receptive area of cortex; LAT, latency, and PK, peak.

ascending route to the centrum medianum and intralaminar nuclei of the thalamus, paralleling the discrete lemniscal pathways to the classic relay nuclei of the thalamus.

Additional records from this diffuse medial ascending system (Fig. 4) emphasized the absence of segregation in it of discharges from sciatic and auditory stimu-

lation (Figs. 3 and 4a to o). Potentials induced from these widely differing peripheral sources were often recorded at the same electrode placement and seemed identical with one another (Figs. 3 and 4a and b). Latencies ranged from 13 to 23 msec., and no systematic difference in latency could be detected in different rostral regions. The potentials throughout tended to be wave-like, with a gradual ascent, late peak time (24 to 30 msec.), and broad base (Fig. 4, a to o), presenting in each of these respects a contrast to discharge usually evoked in classic sensory paths (Fig. 4j, q, r). Aside from these distinctive features, responses of each system were frequently biphasic or triphasic, notched, or irregular in outline. Because of the method of recording, the initial deflection could be either positive or negative, and,
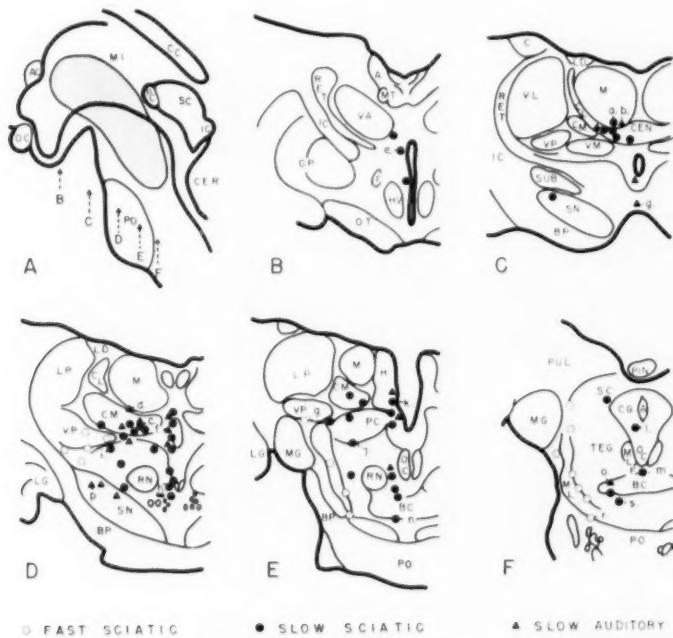

Fig. 3.—Midsagittal reconstruction (A) and cross sections (B to F) of the monkey's brain stem. Stippling in A indicates area from which potentials were recorded; symbols in B to F indicate specific recording sites. Significant abbreviations are as follows: BC, brachium conjunctivum; CEN, nucleus centralis; CG, central gray matter; CL, nucleus centralis lateralis; CM, centrum medianum; M, nucleus medialis; ML, medial lemniscus; SN, substantia nigra; TEG, tegmentum; VP, nucleus ventralis posterior.

in fact, inversion of polarity often occurred as the electrodes descended through an active focus (Fig. 6A and B).

Attention is directed to the records shown in Figure 4s and t, which exhibited initial activity like that in lateral sensory paths and subsequent more prolonged discharge, like that in the medial brain stem. In these instances the recording electrode may have been so placed as to detect both the firing of collaterals from lateral sensory paths and the ensuing reticular discharge it induced.

It can be seen in Figure 3C and D that both sciatic and click stimuli induced discharge in the lateral part of the substantia nigra, indicating afferent connections with this component of the basal ganglia. Both in its long latency and in its wave-like configuration, this activity resembled that evoked from the medial brain stem (Figs. 3 and 4, P).
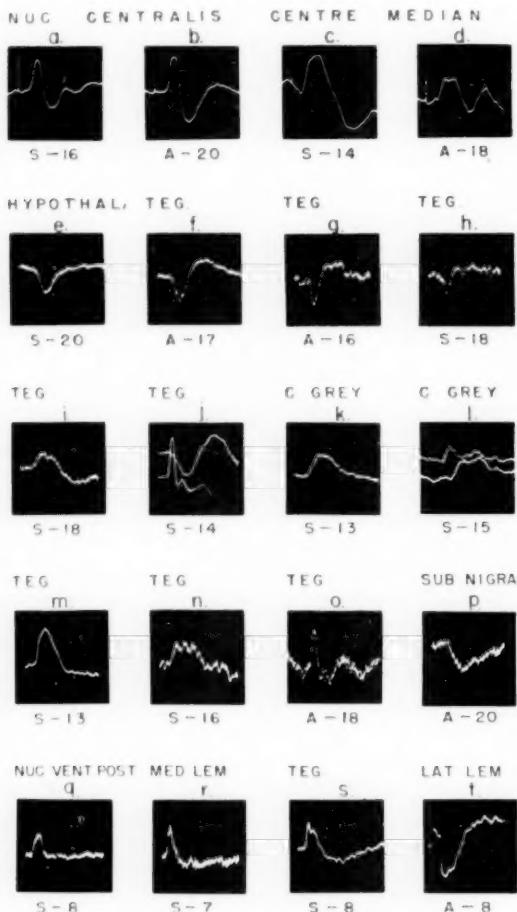
Fig. 4.—Records of potentials evoked in the cephalic brain stem by afferent stimulation. Recording sites are indicated by a lower-case letter above each photograph referring to location in Figure 3; S and A indicate sciatic or auditory stimulation, and the accompanying number indicates the latency, in milliseconds.

In the pontile or mesencephalic tegmentum, potentials were recorded from a number of sites in close proximity to the cerebellar peduncle or red nucleus (Fig. 3D to F). These did not differ from other responses in their vicinity and, since they could still be elicited after cerebellectomy, did not depend upon conduction over cerebellar pathways. The long latency of all responses recorded in the medial brain

stem allowed ample time for afferent impulses to have reached the cerebral cortex over lateral sensory paths and be transmitted back to the brain stem by corticifugal connections. That this did not occur, however, was shown by the fact that the discharge from the medial brain stem was uninfluenced by decortication.
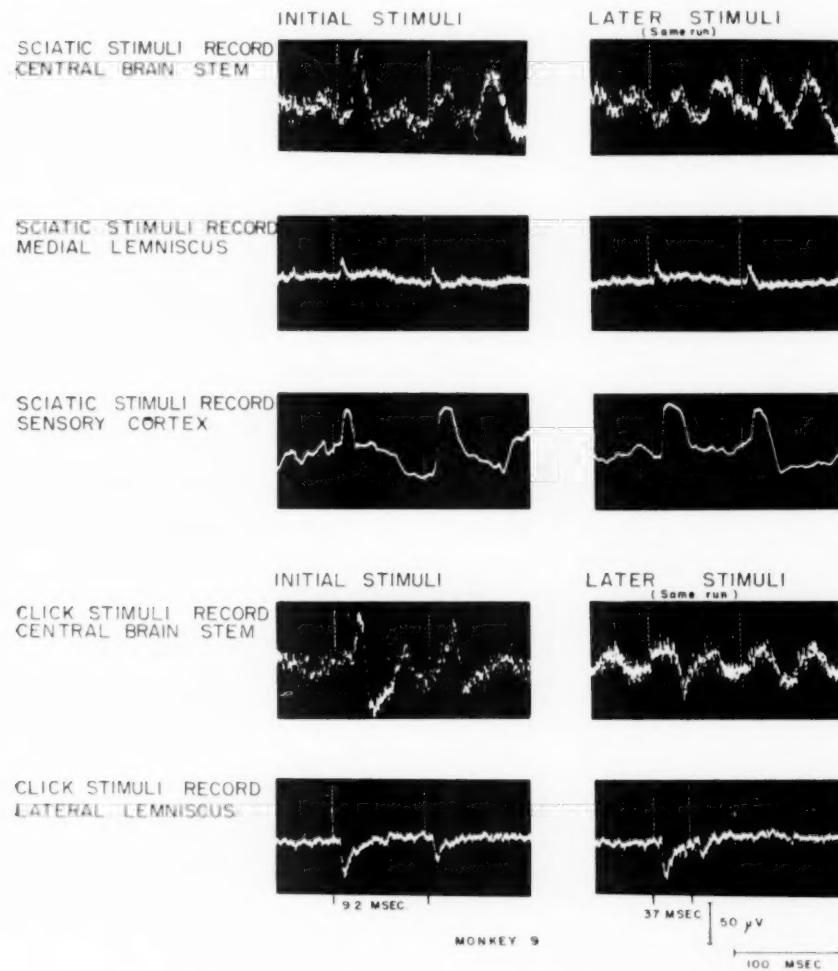
Fig. 5.—Records of potentials evoked by repetitive sciatic (upper three strips) and auditory (lower two strips) stimulation. The left-hand column shows responses to the first pair of stimuli; the right-hand column, responses to the ninth pair of stimuli in the same run.

Further distinctions between medially and laterally evoked potentials were apparent when repetitive stimulation was employed (Fig. 5). When rapidly paired stimuli were consecutively delivered to the sciatic nerve, successive potentials evoked in the medial lemniscus or the sensory cortex were of comparable size as long as
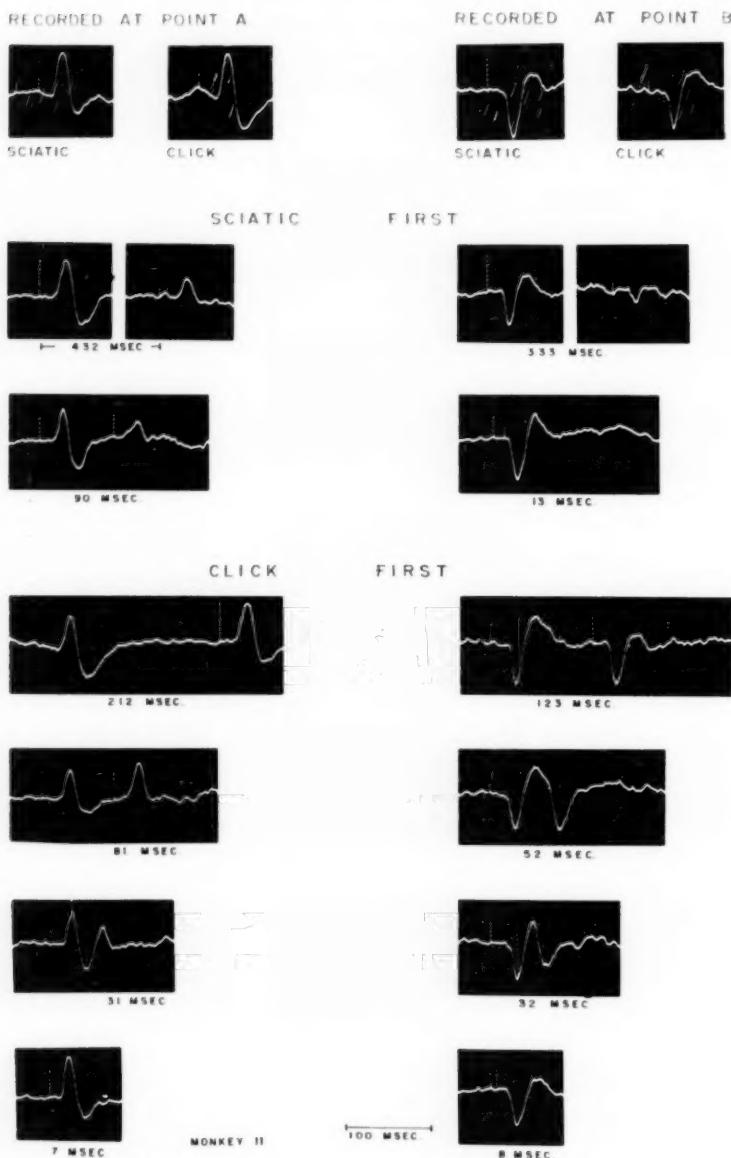
Fig. 6.—Records of potentials evoked in reticular formation from two closely approximated stimuli delivered to the sciatic and auditory systems. Point *B* was 2 mm. below point *A*.

the stimulation was continued (Fig. 5). When paired click stimuli were delivered in succession, the same phenomenon was noted in the lateral lemniscus except that the potential evoked by the second stimulus of a pair showed reduction in size. These lateral sensory pathways continued to respond, however, when stimuli approximated one another as closely as 37 msec. (Fig. 5). On the contrary, in the central brain stem only the first potential was normally evoked, the second being attenuated and all succeeding pairs eliminated when the stimuli were interjected as close together as 92 msec.

When two stimuli were delivered in rapid succession to different sources, further indications for the lack of segregation of modalities in the medial brain stem became apparent. In the lateral sensory pathways, sciatic and auditory potentials were never recorded at the same electrode placement; hence interaction of their evoked responses was impossible. Medially, however, when the electrodes were placed so as to record potentials from both stimuli, an auditory response was found to be completely eliminated when it followed a sciatic potential by 13 msec. and was markedly attenuated when it succeeded the initial pulse by as long as half a second
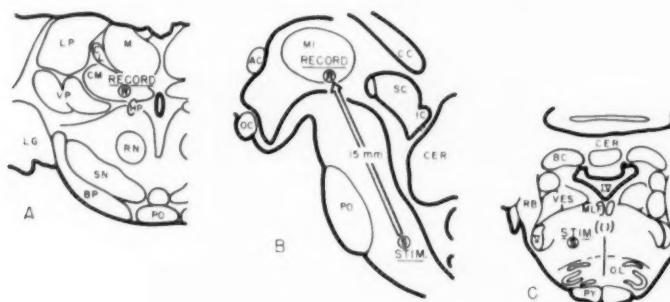

Fig. 7.—Midsagittal reconstruction (*B*) and cross sections (*A* and *C*) of the monkey brain stem, showing stimulating (*S*) and recording (*R*) sites in bulbar reticular formation and centrum medianum (*CM*).

(Fig. 6, upper). A preceding auditory potential was less effective in attenuating a following sciatic response, but the same phenomenon was consistently seen. In this case, the second potential was eliminated when it followed the first by 7 msec. and was reduced when it followed by 212 msec. (Fig. 6, lower). These results indicate that afferent impulses starting from separate receptors converge upon and are conducted forward by a common system of relays in the medial brain stem.

Confirming this view was the finding that afferent potentials evoked in the cephalic portion of the medial system by peripheral stimulation interacted with those induced by direct stimulation in its more caudal part. When electrodes were placed in the centrum medianum of the thalamus (Fig. 7*A* and *B*) and bulbar reticular formation 15 mm. caudad (Fig. 7*B* and *C*), sciatic stimuli evoked discharge at the bulbar recording site after a latency of 10 msec. (Fig. 8*A*) and at the thalamic location after a latency of 15 msec. (Fig. 8*B*). The same thalamic site was fired by bulbar stimulation after a latent period of 5 msec. (Fig. 8*C*). Interaction is illustrated in Figure 8*D*, for when the centrum medianum was fired by sciatic stimula-

tion, it could not be discharged again by a shock delivered to the bulb 40 msec. later. When the procedure was reversed, sciatic stimulation was still able to evoke thalamic discharges 20 msec. after a bulbar shock had done so, and no attenuation was exhibited (Fig. 8E).

A summary of contrasting features of potentials evoked in the two systems reveals that the responses conducted over the lateral pathways exhibited short latencies,
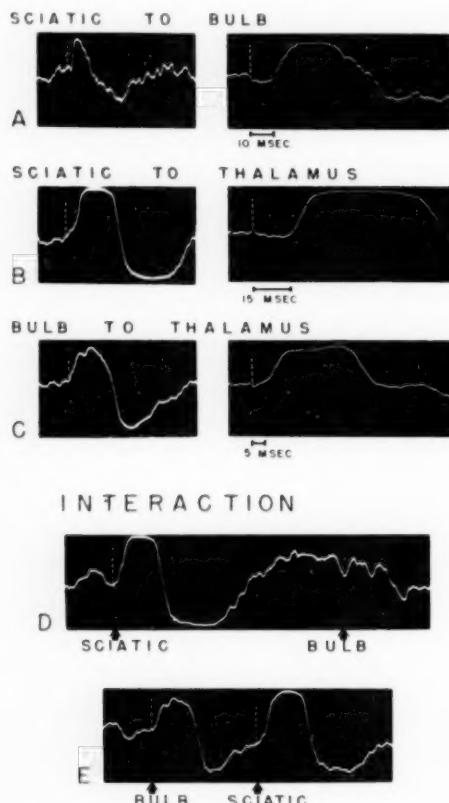
Fig. 8.—Records of potentials recorded in the bulb and thalamus on sciatic stimulation and in the thalamus on stimulation of the bulb at points designated in Figure 7 (A to C). D and E show interaction of bulbar- and sciatic-evoked potentials in the thalamus. Right-hand figures in A to C are fast-sweep records, taken to indicate latency more clearly.

spike-like appearance of the potentials, segregation of responses into discrete pathways, little or no attenuation on repetitive stimulation, and localized distribution in the primary receptive areas of the cortex. On the contrary, centrally mediated potentials displayed long latencies, wave-like outline, lack of modality segregation, attenuation of succeeding responses on multiple stimulation, interaction of discharges evoked from different peripheral sources, and diffuse cortical distribution.

COMMENT

The general outcome of this and related recent studies [7] has been the demonstration of a diffuse system of corticipetal connections ascending through the medial portion of the brain stem. This system supplements that to which our knowledge of sensory neurology has hitherto been confined, the great laterally situated lemniscal systems. Anatomical and functional characteristics of these two systems are in sharp contrast with one another, indicating that they subserve widely divergent functions. Yet a potential from a single peripheral stimulus is propagated simultaneously toward the cortex over the two pathways.

The well-established features of ascending conduction in the great parceled lemniscal systems include modality segregation, rapid direct conduction to contralateral relay nuclei of the thalamus, restricted primary cortical distribution, and responsiveness to repetitive stimuli. Comparably extensive knowledge of propagation of afferent potentials through the medial-brain-stem system is not yet available, but information is accumulating rapidly.

The pioneer studies of Forbes, Morison, Dempsey, and their associates [8] had distinguished earlier the "secondary" cortical response to sciatic stimulation, which, in its medial route through the brain stem, its diffuse cortical distribution, and its long latency and prolonged recovery time, appears similar indeed to evoked potentials studied in the present experiments. The "secondary" response has been considered to reach the cortex by an extrathalamic route from the basal portion of the diencephalon, and such extrathalamic, as well as thalamic, paths for corticipetal conduction have also been demonstrated for the medial reticular system. [5] The "secondary" response is said to be manifest only under conditions of deep barbiturate and tribromoethanol (avertin [*]) anesthesia, however, and in this respect it differs markedly from activity conducted forward in the reticular formation of the brain stem. Susceptibility of the latter activity to anesthesia, to be detailed in a succeeding paper, [9] probably explains why such medial conduction had not earlier been discovered, for, until recently, deep central anesthesia has been used in most studies of afferent conduction within the brain.

The present state of knowledge of the generalized mechanism for corticipetal conduction through the medial brain stem may be assessed. So far as they have been studied, all sensory channels make contributions to this medial system. In addition to its somatic and auditory connections, which have been most extensively investigated, [4] visceral afferent connections from the splanchnic nerve have been demonstrated. [10] Visual connections pass to this region, [4b] and the recent studies of Dell

7. Starzl, Taylor, and Magoun. [4a] French, von Amerongen, and Magoun. [4b] Starzl, Taylor, and Magoun. [5] Moruzzi and Magoun. [6b]

8. Derbyshire, Rempel, Forbes and Lambert. [1] Forbes and Morison. [2] Dempsey, Morison, and Morison. [3] Morison, R. S.; Dempsey, E. W., and Morison, B. R.: Cortical Responses from Electrical Stimulation of the Brain Stem, Am. J. Physiol. **131**:732-743 (Jan.) 1941; On the Propagation of Certain Cortical Potentials, ibid. **131**:744-751 (Jan.) 1941.

9. French, J. D.; Verzeano, M., and Magoun, H. W.: A Neural Basis of the Anesthetic State, A. M. A. Arch. Neurol. & Psychiat. this issue, p. 519.

10. French, von Amerongen, and Magoun. [4b] Aidar, O.; Geohegan, W. A., and Ungewitter, L. H.: Splanchnic Afferent Pathways in the Central Nervous System, J. Neurophysiol. **15**:131-138 (March) 1952. Amassian, V. E.: Fiber Groups and Spinal Pathways of Cortically Represented Visceral Afferents, ibid. **14**:445-460 (Nov.) 1951.

and his associates [11] have shown contributions from vagal and olfactory systems, as well as those of other modalities. Olfactory potentials have also been observed in the medial thalamus by Berry, Hagamen, and Hinsey.[12] This system of medial connections in the brain stem thus appears capable of being excited from all peripheral sources.

In the case of each modality studied, ascending conduction through the medial brain stem is less rapid and, upon initiation, proceeds for a longer time than conduction in the direct lemniscal or corresponding path to the relay nucleus of the thalamus and receiving areas of the cortex. This slowing does not appear attributable to a sorting out of afferent-fiber types entering the brain stem, with those mediating slower conduction ascending centrally. Sciatic stimuli evoking medial discharge in the brain stem do not differ significantly in intensity from those inducing conduction of rapid velocity in the medial lemniscus. Slow conduction in the medial pathway can be accounted for more reasonably by its proposed multisynaptic organization. The absence of long pathways through it is a morphological characteristic of the reticular formation of the brain stem. By direct measurement, transmission from the bulb to the midline of the thalamus may proceed, at its fastest, at the exceedingly slow rate of 3 mm. per second and diminish to velocities below those of even small fiber conduction. Furthermore, the threshold of stimuli inducing such transreticular conduction is not extraordinarily high. In addition, the long recovery time after activity argues for repetitive synaptic transmission along this medial course.

The validity of this concept of multisynaptic conduction is further attested by interaction and occlusion of activity induced in this medial system from different peripheral and central sources. After auditory, visual, sciatic, or splanchnic stimulation, rapidly succeeding excitation of another modality, in any combination, fails to evoke its usual discharge. This convergence of different afferent connections upon common reticular relays indicates that transmission of activity forward is accomplished along channels in which the modality of the initiating signal has lost its identity. In further support of this theory is the present observation that cephalic discharge in this system, induced by direct bulbar stimulation, is obliterated by preceding sciatic-evoked activity.

In the work to date, such sciatic-evoked activity has been preponderant in preventing succeeding activity and has been the most difficult to obliterate by initial stimuli to other afferent or central channels. This phenomenon probably has no more than quantitative significance, direct stimulation of the sciatic nerve in the thigh throwing a larger number of afferent connections into activity than comparable stimulation of the (smaller) splanchnic nerve or than a click or flash of light of moderate intensity. Interaction between sciatic- and bulbar-evoked potentials in the thalamic portion of the system was similarly observed, the same dominance of sciatic response being observed. Obviously, local bulbar stimulation was unable to excite activity in the entire central system equivalent to that induced by sciatic stimulation.

11. Dell, P.: Corrélations entre le système végétatif et le système da la vie de relation: Mésencéphale, diencéphale, et cortex cérébral, J. physiol., Paris **44**:471-557, 1952.

12. Berry, C. M.; Hagamen, W. D., and Hinsey, J. C.: Distribution of Potentials Following Stimulation of Olfactory Bulb in Cat, J. Neurophysiol. **15**:139-148 (March) 1952.

The convergence of afferent discharge from various sources into a common reticular relay has recently been established on a unit basis by Amassian.[13] Recording from the cephalic brain stem into microelectrodes, Amassian observed the discharge of a single reticular neuron fired equivalently by auditory and sciatic stimulation and exhibiting occlusion with rapidly paired stimuli. Both in this and in the present work, one is struck by the failure of paired stimuli to produce facilitation. Intensity of action in this medial-brain-stem system appears, rather, to be registered by desynchronization of its firing. Future work must be devoted to this process, the principles of which do not appear to be readily explained by current neurophysiological axioms.

Considerable interest attaches to the cephalic projection of this medial ascending system to the centrum medianum and intralaminar thalamic nuclei, which are generally recognized as major components of the diffuse thalamic projection system.[14] Studies of this system in both the cat and the monkey have shown it to be obtrusively organized for irradiation of activity to associational thalamic nuclei and to associational areas of the cerebral cortex—in the monkey, primarily to the frontal associational areas, both cingulate and orbital, as well as lateral.[15] Hanberry and Jasper[16] have shown additionally that diffuse thalamic projection influences reach primary receptive areas of the cortex.

What is the functional significance of afferent information delivered to the cerebral cortex by way of these two parallel systems? It seems clear that information delivered over the lateral one is essential for the perception and recognition of stimuli and for their localization. Furthermore, it subserves the discrimination of sensory modality. By contrast, the medial system does not function specifically in any of these capacities, but its ascending influences in initiating and maintaining the conscious state provide the necessary background of activity without which no integrated sensory, motor, or adaptive function is possible. Moreover, the medial system may be involved in management of gradations of attention superimposed upon inattentive wakefulness. These conclusions rest upon the observations that direct stimulation of the medial system induces the electrocortical changes associated with alert attention,[17] while its depression[18] or destruction[19] renders the subject unconscious.

13. Amassian, V. E.: Organization in Somatosensory Systems, Federation Proc. **11**:5 (March) 1952.

14. Dempsey, E. W., and Morison, R. S.: Production of Rhythmically Recurrent Cortical Potentials After Localized Thalamic Stimulation, Am. J. Physiol. **135**:293-300 (Jan.) 1942.

15. Starzl, T. E., and Whitlock, D. G.: Diffuse Thalamic Projection System in the Monkey, J. Neurophysiol. **15**:449-468 (Nov.) 1952.

16. Hanberry, J., and Jasper, H. J.: Independence of the Diffuse Thalamocortical Projection System Shown by Specific Nuclear Destruction, Federation Proc. **11**:64 (March) 1952.

17. French, von Amerongen, and Magoun.[4b] Moruzzi and Magoun.[6b]

18. Penfield, W.: Cerebral Cortex in Man: The Cerebral Cortex and Consciousness (Harvey Lecture), Arch. Neurol. & Psychiat. **40**:417-442 (Sept.) 1938. Cairns, H.: Disturbances of Consciousness with Lesions of the Brain-Stem and Diencephalon, Brain **75**:109-146 (June) 1952.

19. Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B., and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat, Electroencephalog. & Clin. Neurophysiol. **2**:483-498 (Nov.) 1950. French, J. D., and Magoun, H. W.: Effects of Chronic Lesions in the Central Cephalic Brain Stem of Monkeys, A. M. A. Arch. Neurol. & Psychiat. **68**:591-604 (Nov.) 1952. French, J. D.: Brain Lesions Associated with Prolonged Unconsciousness, ibid. **68**:727-740 (Dec.) 1952.

SUMMARY AND CONCLUSIONS

Contrasting features of afferent conduction in the medial and the lateral corticipetal systems were studied in the brain stem and the cortex of monkeys.

Potentials in the classic lateral sensory pathways displayed rapid conduction, segregation of modality, and discrete cortical projection to primary receiving areas of the cortex.

Medially conducted potentials exhibited slower conduction, common transport for all modalities, and distribution to wide areas of the cortex by way of the diffuse thalamic projection system.

Upon peripheral stimulation, a volley of afferent impulses is conducted simultaneously to the cortex by these two systems.

The lateral system appears to subserve perception and the discriminative sensory functions, while the medial system functions in arousing consciousness or alertness, without which the above-mentioned sensory discrimination and effective response would be impossible.

A NEURAL BASIS OF THE ANESTHETIC STATE

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THE RECENT demonstration that potentials evoked by peripheral afferent stimulation may be conducted corticipetally through the central brain stem and medial thalamus, as well as through the great lemniscal fillets and thalamic relay nuclei, has opened to speculation the physiological function subserved by such central pathways.[1] For a number of reasons, it seems feasible to assume that they may be concerned, at least partially, with arousal from sleep or with maintenance of the alert, wakeful state. It has been shown that the region of the central cephalic brain stem, from which potentials evoked by peripheral stimulation can be recorded, is coexistent with that which, when excited by repetitive stimuli, causes arousal of a dormant animal, together with an appropriate change of its electroencephalogram, from a sleeping to a waking state.[2] Furthermore, destruction of this region produces a state of chronic unresponsiveness in the subject.[3]

Analysis of impulses conducted medially has indicated that they contrast sharply in many respects with those transmitted over classic sensory pathways to primary receptive areas of the brain. Thus, potentials recorded medially were found to

1. (a) French, J. D.; Verzeano, M., and Magoun, H. W.: An Extralemniscal Sensory System in the Brain, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 505. (b) Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Collateral Afferent Excitation in the Reticular Formation of the Brain Stem, J. Neurophysiol. **14**:479-496 (Nov.) 1951.

2. Moruzzi, S., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949. French, J. D.; von Amerongen, F. K., and Magoun, H. W.: An Activating System in the Brain of the Monkey, A. M. A. Arch. Neurol. & Psychiat. **68**:577-590 (Nov.) 1952.

3. Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B., and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat, Electroencephalog. & Clin. Neurophysiol. **2**:483-498 (Nov.) 1950. French, J. D., and Magoun, H. W.: Effects of Chronic Lesions in the Cephalic Brain Stem of Monkeys, A. M. A. Arch. Neurol. & Psychiat. **68**:591-604 (Nov.) 1952. French, J. D.: Brain Lesions Associated with Prolonged Unconsciousness, ibid. **68**:727-740 (Dec.) 1952.

exhibit long latencies, wave-like configuration, lack of modality segregation, interaction and attenuation of succeeding responses on multiple stimulation, and diffuse cortical distribution. On the other hand, impulses recorded laterally in the lemniscal and primary sensory areas were found to exhibit short latencies, spike-like appearance, segregation of responses into discrete pathways, little or no attenuation on repetitive stimulation, and localized cortical distribution.[1a]

Current concepts of anesthesia recently reviewed by Butler,[4] Toman and Davis,[5] Wikler,[6] and Himwich[7] were formulated before evidence concerning this medial system was available. The effects of ether and pentobarbital sodium on conduction in this central system was, therefore, investigated in the presently described experiments for any contributions the findings might make to an understanding of the anesthetized state. These experiments were devised to examine contrasting features of potentials conducted via the two routes under various states of wakefulness and of sleep induced with barbital and ether anesthesia.

METHODS

In 10 Macacus mulattus monkeys, the initial exposures were made with the animals under inhalation ether anesthesia, with the exposure margins and pressure points injected with procaine. Subsequent observations were made after immobilization of the animals with decamethonium bromide (syncurine*), respirations being maintained by artificial means through a tracheal cannula.

Single-shock condenser-discharge stimuli (5 volts, 1 msec.) were delivered from a Goodwin stimulator to the central end of the divided sciatic nerve. Auditory stimuli of 1-msec. duration emanating from a pulse generator and amplifier were conducted to the external ear through a hollow ear lug by means of a rubber tube. Potentials were recorded from primary receptive areas (the auditory cortical area was exposed by subpial resection of portions of the overlying parietal lobe) and from the frontal lobes through silver ball electrodes directly applied. Subcortical potentials were recorded by bipolar nichrome wire electrodes oriented through a craniotomy aperture by means of the Horsley-Clarke stereotaxic instrument. Records were made simultaneously on a Grass amplifier and ink writer and on double- or single-beam cathode-ray oscilloscopes. In the latter instances the beam was photographed with a Fairchild camera, either a triggered sweep (speed 3 to 30-msec. per centimeter) or running film (4 to 20 in. per second) being employed.

When potentials suitable for study were evoked in the subcortical and cortical areas of the unanesthetized preparation, the behavior of the discharge was followed during and after anesthetization of the animal. Ether was administered through the respirator tube in some experiments, and pentobarbital was injected intravenously in others. At the completion of each experiment, the electrode placements were verified anatomically.

RESULTS

The recording sites of evoked-potential studies are indicated in Figure 1. They conform closely in location with those previously recorded, both medial and lateral systems being represented. Centrally, auditory responses were evaluated in the

4. Butler, T. C.: Theories of General Anesthesia, J. Pharmacol. & Exper. Therap. **98**:121-160 (April) 1950.

5. Toman, J. E. P., and Davis, J. P.: Effect of Drugs upon the Electrical Activity of the Brain, J. Pharmacol. & Exper. Therap. **97**:425-492 (Dec., Pt. 2) 1949.

6. Wikler, A.: Sites and Mechanisms of Action of Morphine and Related Drugs in the Central Nervous System, J. Pharmacol. & Exper. Therap. **100**:435-506 (Dec., Pt. 2) 1950.

7. Himwich, H. E.: Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Company, 1951.

reticular formation, and sciatic potentials, in the same area, as well as in the centrum medianum. In the lateral sensory pathways, examples of auditory responses were observed in the lateral lemniscus and of sciatic responses in the medial lemniscus. Sciatic potentials were also studied in the leg representation of the postcentral gyrus, as were auditory responses in the primary auditory receptive cortex.

In general, the effect of anesthesia on all responses was similar whether ether or pentobarbital sodium (nembutal* sodium) was employed. As would be expected, the inhalation anesthesia produced a prompter and shorter-lived alteration of the discharge than did pentobarbital, but the degrees of change were comparable with the two types. With ether, considerable effect could be observed after the anesthetic had been administered for 1 minute, while pentobarbital usually required 5 to 10 minutes to produce a change. Similarly, responses frequently returned to a pre-anesthetic state in four minutes after small amounts of ether, while the alteration with pentobarbital often persisted for hours.

Potentials evoked in the lateral sensory pathways were unchanged in latency and in appearance by administration of an anesthetic considerably in excess of amounts
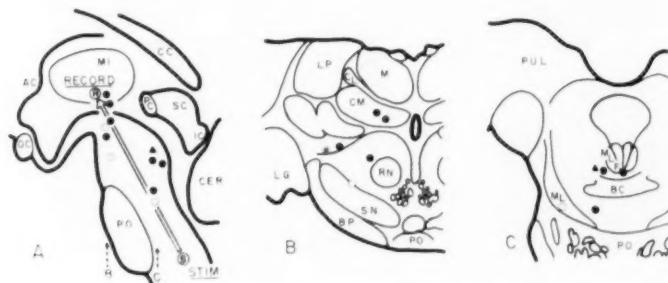

Fig. 1.—Midsagittal reconstruction and cross sections showing sites from which potentials evoked during anesthesia were recorded. Solid circles indicate long-latency potentials; stippled circles, short-latency potentials; triangles, long-latency auditory potentials. *CM*, stands for centrum medianum; *ML*, for medial lemniscus, and *SN*, for substantia nigra.

which caused profound change medially (Fig. 2). On the other hand, centrally located responses in the pons, midbrain, or thalamus, whether emanating from auditory or from sciatic stimuli, were profoundly altered by both anesthetic agents. This alteration was manifested only in the configuration of the potential, as its latency appeared to show little, if any, effect (Figs. 3 and 4). As the anesthesia progressed, the centrally located response diminished in amplitude, until it completely disappeared at the deepest stage. Similarly, the potentials progressively returned frequently to their initial amplitude as the anesthetic effect was dissipated (Figs. 2, 3, and 4). The deterioration of the responses from the central cephalic brain stem corresponded with appropriate slowing of spontaneous electroencephalographic activity in this area and in the cortex as sleep was induced (Fig. 6). These alterations were uninfluenced by decortication (Fig. 4) or cerebellectomy (Fig. 5).

The same effect was observed in potentials evoked in the medial thalamus from stimulation in the bulbar tegmentum some 15 mm. caudal to the recording site (Fig. 1). As with responses resulting from peripheral excitation, these potentials
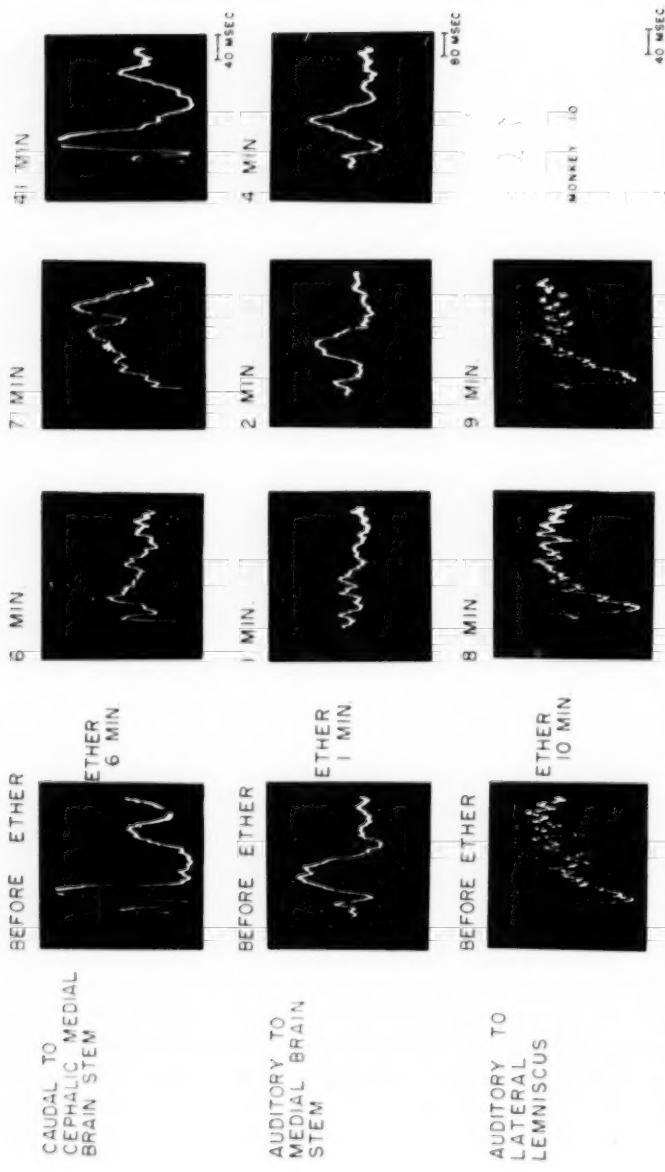
Fig. 2.—Oscilloscopic records made from various points in the brain stem, showing effect of ether on potentials evoked from designated sources. Records are to be read from left to right.

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MID- & ROSTRAL-
TEGMENTUM

MID-TEGMENTUM
& SENSORY CORTEX

A. BEFORE
NEMBUTAL®

B. 0.5 cc. NEMBUTAL®

C. 1 cc. NEMBUTAL®

D. 1.5 cc. NEMBUTAL®

E. 2½ HRS AFTER D

40 MSEC.   MONKEY 2
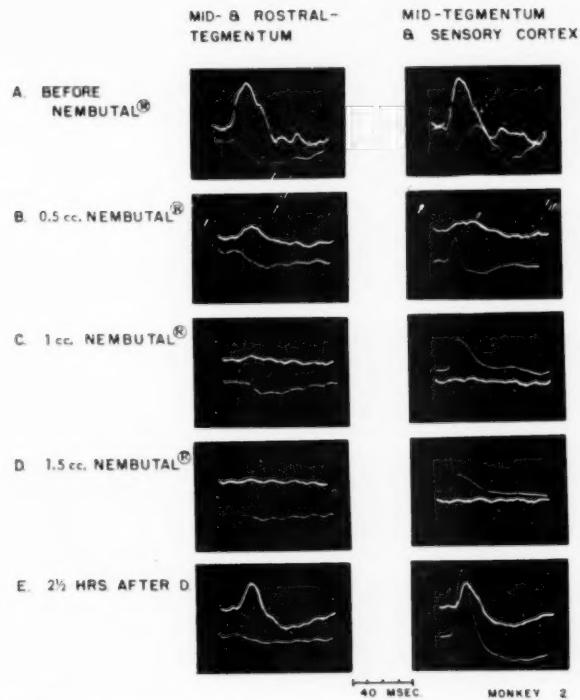
Fig. 3.—Oscilloscopic tracings recording potentials evoked by sciatic stimulation in the brain stem before and successively after the administration of pentobarbital sodium. Records are to be read from top to bottom. In the left column, both beams illustrate activity in the central brain stem; in the right column, the heavy beam records from a similar area and the fine beam, from the sensory cortex.

A. BEFORE
NEMBUTAL®

E. 2½ HRS.
AFTER C.

B. AFTER 1cc.
NEMBUTAL®

F. 1½ HRS. AFTER
DECORTICATION

C. AFTER 2cc.
NEMBUTAL®

G. AFTER 1cc.
NEMBUTAL®

D. 1 HR. AFTER C.

H. AFTER 2cc.
NEMBUTAL®

40 MSEC   MONKEY 5
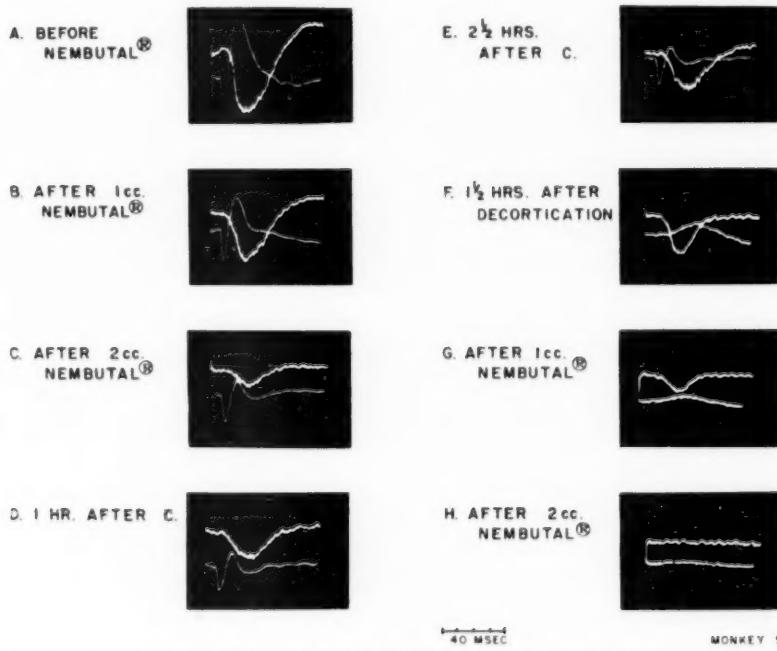
Fig. 4.— The heavy tracing records evoked potentials from sciatic stimuli in the central brain stem, and the fine line, similarly evoked potentials from the sensory cortex.

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diminished (Fig. 7) and disappeared (Fig. 2) as anesthesia progressed, only to return as the animal recovered.

Discharges evoked by sciatic and auditory stimulation in the appropriate primary sensory areas of the cortex behaved somewhat differently in response to anesthetization of the animal. Sciatic responses in the postcentral gyrus were most character-
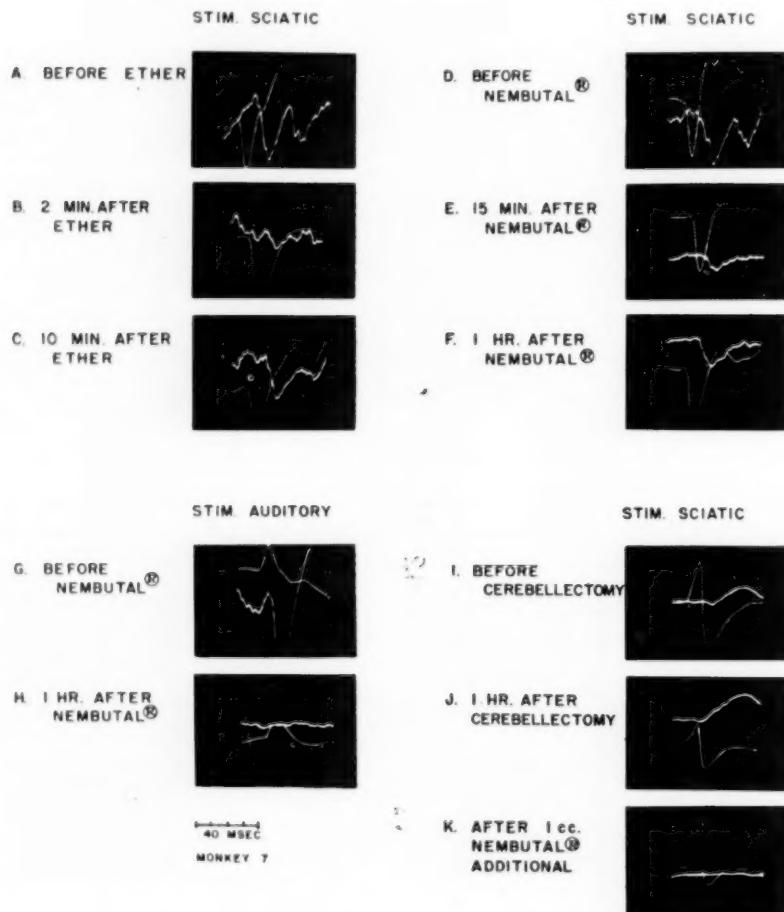
Fig. 5.—The fine line records evoked potentials in the sensory cortex, and the heavy line in the central brain stem, in all tracings.

istic and will be described in some detail, although similar tendencies were observed in auditory responses. Sciatic responses were characteristically multiphasic in the unanesthetized preparation. The initial event was always represented as a sharp spike, although this deflection could be directed either downward or upward. Immediately following this spike was a wave of opposite polarity and usually larger amplitude, succeeding which a third, slowly developing wave could occasionally be seen.

As anesthesia deepened, the initial spike deflection consistently increased in amplitude, and usually in duration, coincident with the decline of the medial-brain-stem response (Figs. 3, 4, 5, and 6). The change in the cortical spike reached a maximum, sometimes amounting to twice normal size, at a stage corresponding to deep depression of the animal and thereafter returned to its preanesthetic appearance. Simultaneously with these events, the second cortical deflection usually diminished in amplitude, finally disappearing (Figs. 4, 6, and 7), although occasionally this effect was incomplete (Fig. 6). The third deflection always disappeared. The
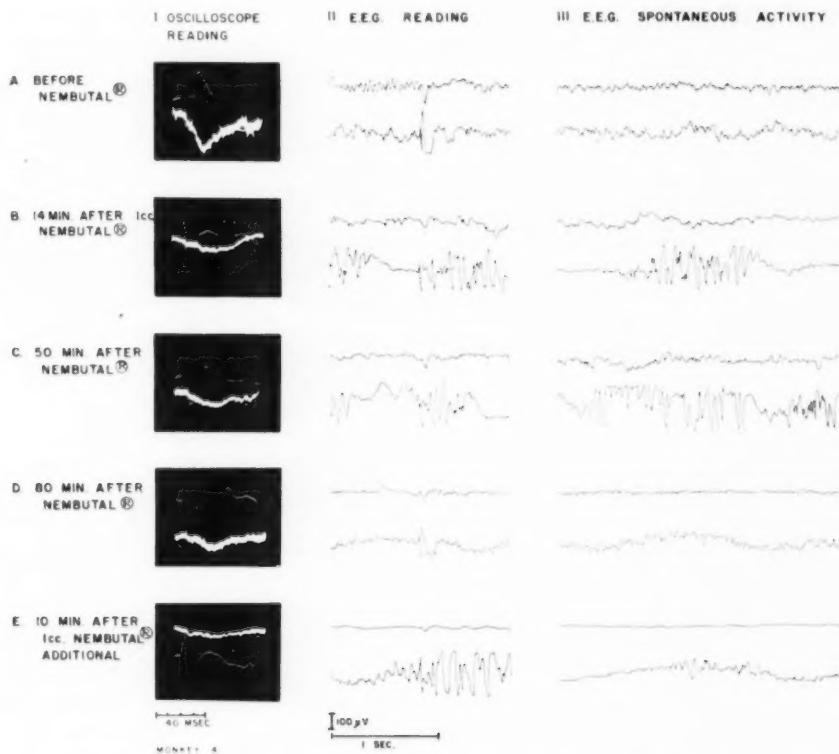
Fig. 6.—The fine line on the oscilloscopic photographs and the lower tracing in the electroencephalographic readings record evoked potentials from sciatic stimulation (and spontaneous activity) in the sensory cortex after administration of pentobarbital, while the heavy oscilloscopic line and the upper tracing in the electroencephalograms represent activity in the central cephalic brain stem.

effects described were optimally seen during pentobarbital anesthesia, owing apparently to its more deliberate effect; but the ether response was generally the same (Fig. 5). Although the alteration of the initial spike, and even, infrequently, the second wave of the cortical response, was occasionally minimal, attention is directed to the fact that the initial spike deflection in the primary sensory cortex was never diminished by anesthesia (Fig. 6).

As may be seen in the electroencephalographic tracings, the induction of anesthesia was associated also with the appearance of repetitive after-discharge in the sensory cortex,[8] following the initial evoked potential (Fig. 6 *II*). This response occurred at a state of anesthesia in which spontaneous spindle bursts, indicating sleep, occurred (Fig. 6 *III*).

In summary, therefore, it was observed that evoked potentials recorded in the lateral sensory pathways and the initial event in the primary sensory cortex were unaltered, or in the latter case even augmented, by anesthesia. On the other hand, responses evoked in the central cephalic brain stem by peripheral or central stimulation were progressively diminished or obliterated during deepening depression of the animal. Such diminution was also observed in the later events of the complex potential in the sensory cortex.

A   BEFORE ETHER

B   2 MIN AFTER ETHER

C   4 MIN AFTER ETHER

D   IO MIN AFTER ETHER

MONKEY II   30 MSEC
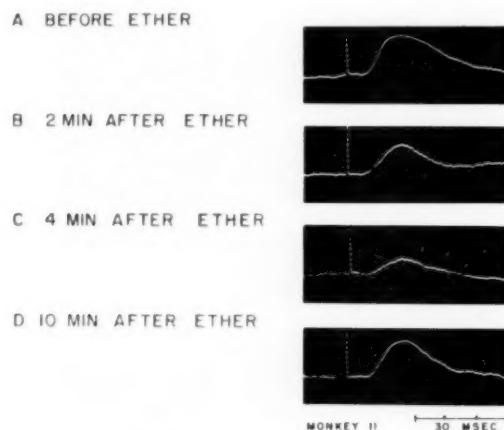
Fig. 7.—Effect of ether on conduction of potentials from posterior to anterior brain stem. The stimulating point is centrally located at *S*, and the recording point at *R*, in Figure 1.

COMMENT

It has been indicated earlier that afferent potentials conducted medially in the brain stem and those transmitted laterally in the great sensory pathways differ in a number of fundamental characteristics. From the results of these experiments, it is apparent that the alteration in conductivity of these transmitting systems on anesthetization of the animal presents an additional feature in which they are diametrically at variance.

Conduction in the central brain stem was found to be effectively blocked by both ether and pentobarbital sodium in a stage of anesthetic depression at which transmission of impulses laterally was unimpeded. This blocking was manifested by an alteration in the intensity of the response, as indicated by a progressive diminution in amplitude of the evoked potentials, rather than by a change in rapidity of their

8. (*a*) Chang, H. T.: Repetitive Discharges of Cortico-Thalamic Reverberating Circuit, J. Neurophysiol. **13**:235-258 (May) 1950. (*b*) Bremer, F., and Bonnet, V.: Interprétation des réactions rythmiques prolongées des aires sensorielles de l'écorce cérébrale, Electroencephalog. & Clin. Neurophysiol. **2**:389-400 (Nov.) 1950.

transmission, their latencies being unaltered. This effect could be demonstrated whether the discharges were evoked by peripheral stimulation or by excitation applied centrally to the bulb at a point caudal to the recording electrode in the medial thalamus. This anesthetic effect would, therefore, appear to be exerted on the central brain stem itself rather than on collateral fibers coursing to it from the long sensory fillets.

It has been demonstrated that impulses propagated corticipetally over the medial and lateral brain-stem pathways are of identical origin, as evoked potentials can be recorded throughout the extent of each from a single peripheral stimulus. Moreover, the threshhold of such stimuli was found to be identical with that required to excite sensory fibers in peripheral nerves, the conclusion being that a difference in latencies of potentials in the two systems is not a factor of fiber size, and hence of excitation of separate neuronal elements. There is no indication, therefore, that anesthesia produces its effect by selectively blocking sensations of separate modalities conducted in fiber systems of distinct size or transmission properties. It appears, rather, that a single impulse traverses both systems in its corticipetal transport and that only transmission coursing centrally is blocked by anesthesia. In addition, as latencies were unaltered by anesthesia, it seems unlikely that the agents administered produced their effect by altering the nerve fiber itself, hence depressing the rate at which it is capable of transmitting electrical change.[9] The recent study of Larrabee and Posternak [10] indicates that the effect of central anesthetics on nerve-fiber conduction proceeds without reference to fiber diameter or velocity of fiber conduction. Furthermore, they have shown that synaptic transmission is blocked long before fiber conduction is affected.

Previous evidence has indicated that transmission in the medial brain stem is mediated by multineuronal units, in contradistinction to that in lemniscal pathways, where there are relatively few synaptic relays. The present findings would indicate that the differential susceptibility to anesthesia of these two systems is dependent upon the highly complex interneuron organization of the medial one. Bremer,[11] Forbes and associates [12] and Bárány [13] have previously emphasized the susceptibility of complex interneuron systems to anesthesia.

The undiminished persistence of laterally conducted impulses to the primary receptive areas of the cortex after the administration of anesthesia confirms this contention. The alteration in appearance of these cortically evoked potentials by depressants, moreover, may have a similar basis of explanation. The augmentation of the initial evoked cortical spike, coincident with the progressively diminishing amplitude of the centrally recorded response as anesthesia deepens, certainly indi-

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10. Larrabee, M. G., and Posternak, J. M.: Selective Action of Anesthetics on Synapses and Axons in Mammalian Sympathetic Ganglia, J. Neurophysiol. 15:91-114 (March) 1952.

11. Bremer, F.: Différence d'action de la narcose étherique et du sommeil barbiturique sur les réactions sensorielles acoustiques du cortex cérébral: Significance de cette différence en ce qui concerne la mécanisme du sommeil, Compt. rend. Soc. biol. 124:848-852, 1937.

12. Forbes, A.; Battista, A. F.; Chatfield, P. O., and Garcia, J. P.: Refractory Phase in Cerebral Mechanisms, Electroencephalog. & Clin. Neurophysiol. 1:141-175 (May) 1949.

13. Bárány, E. H.: Theoretical Note Concerning Action of Drugs on Central Nervous System, Arch. internat. pharmacodyn. 75:222-226 (Nov.) 1947.

cates that lemniscal potentials reach the neopallium with unimpaired, or even augmented, intensity. That this portion of the potential is associated with the local arrival of excitation is clear. Whether it is a reflection of events occurring in the terminal axon [14] or a "source"-and-"sink" phenomenon resulting from transsynaptic discharge of granular cells in the fourth layer of cortex [15] cannot be amplified from these data. The deterioration of succeeding events in these complex cortical potentials in such circumstances, however, parallels rather the course of events observed in the behavior of the deeper responses in that the second and third waves of the multiphasic cortical response usually declined and disappeared. The effect has been previously described by Heinbecker and Bartley,[9] although they considered it to be the result of progressive blocking of conduction in different-sized neurons. Whether these waves in the unanesthetized state represent locally induced phenomena [15] or are the result of delayed arrival of electrical excitation via the central brain stem cannot now be determined, although the latter possibility would seem unlikely, as time relationships between the two events are not entirely compatible with this explanation. Whatever their basis, these wave responses no doubt represent multisynaptic or interneuron phenomena, and hence, as in the perhaps similarly organized deeper structures, would be expected to be depressed by anesthesia.

Two suggestions, therefore, present themselves in the explanation of the anesthetized state. One is the reduction of sensory input to cortex over lateral sensory paths or the failure of the cortex to make effective consequent use of it. The other would exist if the subject was rendered unconscious and, in consequence, was unable to make use of sensory information which arrived in the cortex without impairment. These possibilities are not entirely dissimilar, and it is likely that both are involved. The observation that anesthesia produces a prolongation of recovery time in thalamic relay nuclei [16] indicates that repetitive lemniscal discharge fails to reach the sensory cortex in normal quantity, although single shocks are conducted without impairment. In addition, the observations reported here, as well as those of Bremer and Bonnet [8b] and of Chang,[8a] emphasize that local cortical events excited by afferent volleys are depressed by narcosis.

The more significant alteration, however, would appear to be the reduction, and, with surgical levels of anesthesia, the block, of impulses conducted corticipetally through the medial-brain-stem system. As previously mentioned, it has been possible to render animals permanently unresponsive or "unconscious" by placing electrolytic lesions in the central cephalic brain stem. In connection with such experiments, it was adduced that this behavioral state resulted from irreversible elimination of desynchronizing influences on cortical and diencephalic structures normally exerted by the activating system. It appears that a similar, but reversible, mechanism participates in an explanation of the anesthetic state.

14. Forbes, A., and Morrison, B. R.: Cortical Response to Sensory Stimulation Under Deep Barbiturate Narcosis, J. Neurophysiol. 2:112-128 (March) 1939.

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16. Marshall, W. H.: Observations on Subcortical Somatic Sensory Mechanisms of Cats Under Nembutal Anesthesia, J. Neurophysiol. 4:25-43 (Jan.) 1941. Jarcho, L. W.: Excitability of Cortical Afferent Systems During Barbiturate Anesthesia, ibid. 12:447-457 (Nov.) 1949.

SUMMARY AND CONCLUSIONS

The effect of anesthesia was studied on potentials conducted in the medial and in the lateral pathways of the brain stem to the cortex.

Impulses propagated over the medial system were blocked after the administration of ether or pentobarbital sodium to the animal.

Upon anesthetization, laterally conducted impulses reached the sensory cortex with unimpaired, or even augmented, intensity, although later cortical events in the complex evoked potential were altered.

The evidence suggests that the central-brain-stem system has a multisynaptic interneuronal organization, making it more susceptible to anesthetic blockade than the paucisynaptic lateral pathways. Similarly, interneuronal systems in the cortex would seem to be influenced by the anesthetic agents employed.

It appears that depression of activity in these areas participates to a considerable degree in production of the anesthetic state.

Society Transactions

Evolution of Basic Patterns of Movements in Man: Their Diagnostic Significance in Spastic Paralysis. Dr. Temple Fay.

Observations on basic patterns of movement manifested in man were presented in the light of their evolutionary significance. Five characteristic patterns, corresponding with neurostructural levels evolved in vertebrates, were selected for study.

Functional-environmental considerations, as well as comparative neuroanatomical correlation, indicate that levels above the primitive, cord-medulla structure serve to modify, inhibit, repress, and control gross mass patterns of movement of the extremities (swimming), originally designed for trunkal progression.

Skills acquired during the evolutionary process are not new movement patterns; on the contrary, they represent higher controls and modifications of original, basic extremity facility. Crude power movements are toned-down, transformed, and blended responses from super-inhibitory centers, rather than "initiated-stimulated" responses.

Release of higher controlling levels permits desired "patterns of movement" to emerge under guidance or cybernetic sensory stimuli. Powerful mass reflexes, single or combined, usually classified as "pathological reflexes," become important adjuncts to rehabilitation.

Diagnostic-therapeutic values of "pattern movements" were discussed, and techniques of training and treatment were presented.

The "tonic neck," "postural," "sustaining," and "defense" reflexes may be conditioned to serve a purpose in the rehabilitation of spastic paralysis. The author termed this method of functional substitution "capturing the reflex."

Complications Involving the Central Nervous System of Certain Diseases of the Viscera. Dr. T. K. Rathmell, Trenton, N. J.

One of the penalties of the modern era of specialization in medicine is the physician's occasional failure to evaluate the total structure and physiology of the human organism before formulating his diagnosis, prognosis, and treatment. Several illustrative cases were presented.

1. A case of recurrent hemiplegia with old and recent areas of encephalomalacia of the internal capsule in which autopsy showed congenital cystic lesions of the kidneys, liver, spleen, lungs, and pancreas, clinically diagnosed.

2. A case of undiagnosed anemia and hemiplegia with autopsy findings of subacute bacterial endocarditis and a mycotic aneurysm of the circle of Willis, clinically undiagnosed.

3. The case of an infant aged 10 months in which the clinical diagnosis was "rubber baby" and autopsy showed changes in the central nervous system compatible with a diagnosis of amyotonia congenita, or Oppenheim's disease. Longitudinal sections of the rectus abdominis showed peculiar muscle knots. Their role in the symptomatology of amyotonia congenita, if any, appears to be unknown. Indeed, information of muscle pathology in general could well be enlarged.

Specialists, in their search for the minute, must always maintain an appreciation of the general picture which the patient presents if medicine is to advance. Studies of the supposedly well-known neurological entities may reveal new facts.

Transorbital Lobotomy in Chronically Disturbed Patients. Dr. William Wilson, Philadelphia, and (by invitation) Dr. A. R. Pittman, Dr. R. S. Garber, and Dr. R. E. Bennett, Trenton, N. J.

The authors presented the results obtained in 400 cases of transorbital lobotomy over two and one-half years. The patients chosen were those who failed to improve under any other type of psychiatric therapy and whose condition was considered hopeless. More recently, several psychoneurotic patients had been operated upon.

In round figures, 20% had shown sufficient improvement to leave the hospital; the results for 28% were considered excellent, but they had remained hospitalized, in many cases owing to lack of friends or family to provide a home for them; 24% had shown fair results, and 26% were unimproved. The operative mortality was 2%. No patient had beeen made worse by the operation. All types of psychiatric patients were included in the series, but the predominant diagnosis was schizophrenia.

From the foregoing figures it is obvious that great psychiatric gains are obtained by a procedure of this type; in addition, the economic factor is of paramount importance to those practicing in large state psychiatric hospitals.

We urge that this operation be considered for all patients who have failed to respond to other forms of psychiatric therapy in a year.

<center>DISCUSSION</center>

Dr. Walter Freeman, Washington, D. C.: Some of my neurological colleagues in Washington are concerned over the hazards of the so-called blind approach in transorbital lobotomy. I believe they would be less so if they would examine the frontal view of the arteriogram or the carotid angiogram, which shows a large separation between the branches of the anterior and the middle cerebral artery, representing the white matter and the ventricles. The bleeding in transorbital lobotomy arises mostly from small arteries at the base of the frontal lobe, where the arteries are caught between the leucotome and the orbital plate. Only the heavy-handed would wound either the anterior or the middle cerebral artery.

I have data now upon 2,000 lobotomy operations on some 1,800 patients which show the relative hazards of prefrontal lobotomy and transorbital lobotomy. The over-all mortality is 6.3% for prefrontal lobotomy, as against 1.7% for transorbital lobotomy. While hemorrhage is the outstanding cause of operative deaths in transorbital lobotomy (1%) and its incidence is only half as great in prefrontal lobotomy, nevertheless in the latter operation misplaced incisions and infections are relatively commoner, whereas in transorbital lobotomy their incidence is less than 0.1%.

Analysis of death occurring long after operation shows a preponderance of circulatory deaths in the cases of prefrontal lobotomy, probably reflecting the longer follow-up period, and a preponderance of malignant disease in the cases of transorbital lobotomy, showing that this operation has been used to alleviate distress in a great many cancer patients who have later died. Transorbital lobotomy is the operation of choice for these patients, since prefrontal lobotomy is needlessly drastic.

I have divided the complications and sequelae of surviving patients into physical and social.

Foremost among the physical complications I should list a convulsive tendency (even though only one or two convulsions are recorded), occurring in 25% of the prefrontal group. Exclusive of patients who had convulsions before operation, the corresponding figure for the transorbital series is less than 1%. Approximately the same figures hold true for incontinence lasting for a month or more. Hemiplegia was less frequent after transorbital lobotomy than after prefrontal lobotomy. The "frontal-lobe syndrome" was noted in about 10% of cases of prefrontal lobotomy and in 1% of the transorbital series, this term being used to denote a combination of irresponsibility and indolence, interfering seriously with adjustment in the home. A gain of 50 lb. (22.7 kg.) in weight was found much oftener in the prefrontal than in the transorbital series. Alcoholism, illegitimate pregnancy, and suicide were about equally represented. The only homicide was perpetrated by a lobotomized patient who underwent prefrontal lobotomy about five years ago for relief of an anxiety state.

These figures serve to indicate that transorbital lobotomy is much the safest of the operations on the frontal lobe. In the past three years this operation has replaced prefrontal lobotomy, the latter operation having been performed in only three cases.

Dr. Rudolph Jaeger: As a basis for my comments on transorbital lobotomy, I shall show a slide of the sliced brain of a victim of this "ice-pick" operation performed at a psychiatric hospital. Death was due to massive hemorrhage from a tear in a major vessel. It will be also noted that there is a dissecting clot on the opposite side in the same location. When a psychiatric patient, with a curable lesion, is operated on in nonsurgical surroundings by a psychiatrist or a neurologist, admittedly without neurosurgical training or equipment, what chance has he of surviving such an acident? The boldest, most skilled neurosurgeon would no more operate under such conditions than would a famous violinist if sober play a selection from a master at 2 a. m. in a barroom on a borrowed violin.

What arguments can be brought forth in favor of an operative method with so little scientific chance of being a generally safe procedure?

1. The equipment is simple; only one instrument is needed. This argument answers itself.

2. Removal of hair is unnecessary. I ask: Is the temporary loss of some hair a valid reason for performing an operation in a nonsurgical, hazardous manner?

3. The operating physician's (psychiatrist's) time need not be seriously interfered with in performing this operation. We hear it repeatedly mentioned that the operation requires only a few minutes and often the psychiatrist can perform many operations in a matter of minutes. Why need asesmbly-line, factory methods be applied to a procedure which has inherent in it the potentials for such serious results as death or lifelong convulsions? Once this operation has been performed, its results are as irrevocable as extinguishing the breath of life itself.

4. The operator need not be a surgeon, trained or otherwise, although it must be admitted that the procedure requires the making of a massive brain-center laceration after passing through conjunctiva, orbital content, skull, dura, and cerebral cortex and very near, or at times through, the middle, anterior cerebral, and carotid arteries, to say nothing of numerous large veins that must be ruptured. No step of this procedure permits the careful avoidance of surgical disasters that must often occur in a blind, deep-cutting operation of this type.

It has been alleged that the mortality is less than that with the conventional method. This statement does not conform to the comparative figures of which I have knowledge. Any experienced physician knows too well the pitfalls of statistics and the methods by which they are made.

Can you believe that any operation performed blindly by puncturing all the tissues that the ice pick must pass through is as safe as a procedure carried out through open exposure and under direct vision, where any excessive hemorrhage can be readily observed and stopped? The possibility of death from hemorrhage when the operation is performed by a neurosurgeon is slight, for hemorrhage is his daily problem in every operation on the brain. He is trained to recognize and control it. The performance of a brain operation of the magnitude and consequence of lobotomy without adequate equipment and surgical skill—an operation requiring the making of a compound wound of the cranium and leaving a massive bloodless laceration of the brain—is neither scientifically nor morally justified.

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mella, M.D., *President, in the Chair*
Regular Meeting, Nov. 14, 1952

Psychophysiological Studies of Fistulous Openings into the Gastrointestinal Tract.
Dr. Sydney G. Margolin, New York.

The author stated that for the past five years the psychiatric service at Mount Sinai Hospital, New York, had been doing research on the reciprocal influence of the unconscious on the functional changes in the viscera by studying patients with fistulas. He presented a number of typical reactions and behavioral adjustments in patients with fistulous openings. Gastrostomy, ileostomy, and colostomy fistulas produce certain attitudes, with common features. Patients with tracts to secretory organs, e. g., the pancreas, react differently.

In this study it was investigated especially how the presence of the fistula itself profoundly influences through psychological mechanisms the behavior of the organ it displaces. Fistulas are structures in which mucous membranes are in contact with the skin. The patient is deprived of a body function, such as eating or defecating. Therefore, he must "discover" the new organ, very much as the infant grows gradually aware of the gratifications inherent in the mouth, anus, and urogenital structures. The immediate reaction of the patient is one of profound bodily insult and disability. He then "discovers" or integrates the fistula into the body economy by a displacement or a reactivation of an infantile attitude that once prevailed in the organ whose functions have been surgically disrupted.

The function that is displaced in these patients appears essentially to be a sexual, or erotic, one—vaguely masturbatory or autoerotic. It is accompanied by day dreams rapidly repressed, and therefore unconscious. These can be elicited by means of psychoanalytic techniques.

When the erotization of the fistula occurs, it is accompanied by a successful adaptation to the lesion and a favorable change in its functional replacement of the organ.

The other group of patients, with fistulas to secretory organs, have a different problem and adapt somewhat differently.

Attention was called to the use of psychoanalytic techniques to demonstrate mechanisms and processes of which the patient is unaware, and therefore cannot describe spontaneously. Psychoanalysis as an investigative technique also carries with it valuable therapeutic potentialities, as illustrated in one case.

DISCUSSION

DR. EDWARD WEISS: The study of the stomach preceding this investigation, concerning which Dr. Margolin showed us a few slides, represented one of his first important contributions to this new psychosomatic research, in that the combination of psychological investigation and physiological research constitutes, in the truest sense, a psychosomatic approach in research medicine. In other words, it represents the confluence of a broad stream of physiological and psychological knowledge that stems from the investigations and psychoanalyses. In this comprehensive approach, a detailed physiological investigation interpreted with psychological studies, one does not study the soma less but the psyche more. Dr. Margolin's work may be thought of as the illumination of the art of medicine, because he has subjected the patient-doctor relationship to scientific scrutiny. One of the first points he has made in this regard, and I think it is important, is that of the obtrusion of the "device" in psychosomatic research.

He has studied the gastrointestinal tract, and he has pointed out many reasons that the instincts are so important in relation to this tract, and how, when their natural outlets are interfered with, personality changes are bound to occur. This is a lesson that has only lately been learned in medicine. It touches on the whole problem of specificity in psychosomatic medicine. Whether the personality is closely related to a specific disease or is unrelated to specific stresses and strains is a question very important in psychosomatic research.

DR. WILLIAM T. FITTS: The frequency of these fistulas in a general hospital may be of interest. There is a greater number of colostomy fistulas, approximately 75%, usually as a result of operation for carcinoma of the colon, carcinoma in men occurring most frequently in the colon. When the carcinoma involves the rectum, the patient frequently is left with a permanent colostomy. The other types, ileostomy fistulas and openings into the stomach, make up about 7% and 5% respectively. This leaves a much smaller percentage of esophagostomy fistulas and of surgical openings into the duodenum or jejunum. Because patients with such lesions are few, they would not become a problem to the psychiatrist, as the others would. In the first place, ileostomy is usually done for ulcerative colitis, and for a time for regional ileitis. Colostomy, on the other hand, is almost always done for cancer, and the patient is more likely to be a stable person, for carcinoma of the colon has a good prognosis. Ileostomy patients are much more difficult to cure. Ileostomy frequently has complications, such as prolapse, or often difficulty with the ileostomy stoma itself.

My colleagues and I have been interested in the care of the colostomy patient. I think it important that such a patient not wear a bag. The ileostomy patient, because of the liquid character of the excretions, has to wear a bag. This is a disadvantage, even though the bag can be adapted to his needs and can be made more comfortable than formerly. The colostomy

patient should not wear a bag, for it is much more malodorous and increases the danger of pro-lapse. We make it a point to have one person, probably a nurse, begin a few days after the colostomy to instruct the patient in the care of his colostomy fistula. The patient is given a mimeographed form, which tells him that it will still be possible for him to carry on most of his normal activities and teaches him care of the colostomy fistula. He can irrigate it frequently—every two or three days. We say, "Colostomy is necessary to make some patients well. The operation merely changes the position of the rectum and creates a new abdominal opening. It need not be a nuisance. With proper care, there is no unpleasant odor. Eighty per cent of our patients continue to carry on regular business and social activities. Many play golf, go bathing, etc. It is important to learn to control your colostomy opening. It is necessary to be strict about regulation of diet and to learn to care for the opening at a regular time."

I do not mean that most patients would not like to have another anastomosis done, or that they are not inconvenienced by the colostomy fistula. However, I did have a patient who had been operated on, successfully, for carcinoma of the descending colon 10 years ago and who still had his rectum; it would therefore have been feasible to make a new anastomosis. I asked him whether he would like to have it done. He replied, "It's much easier this way." I irrigate it only every three days, and it's easier to care for."

Dr. Howard D. Trimpi: Dr. Bacon and I have been very much interested in the problem of colostomy and ileostomy. We started out under the impression that colostomy would bring about personality changes in patients with cancer. For that reason, Dr. Bacon worked out a modification of the Babcock operation which preserves the continuity of the bowel. In this we made a new rectum, in order to avoid an abdominal colostomy fistula, and simply had a perineal colostomy opening. We wanted to make the new opening one that could function well enough for the patient to go out and have a fairly good degree of rehabilitation. We had to return to use of the Miles operation, which in our hands has been greatly amplified, and is often extended to include the bladder and the genital organs; and sometimes we do an operation called "viscerectomy." We found that rehabilitation in patients in whom we had preserved the rectum and the rehabilitation in others in whom we had done the usual type of colostomy were just about the same. We found, to our amazement, that we did not get this profound personality change at all. Our colostomy patients were rehabilitated very nicely.

We are more concerned with the ileostomy patients. There is a striking difference between patients having ileostomy for ulcerative colitis and those having the operation for polyposis. The latter group is small; we have had six or eight patients. However, their rehabilitation has been much more rapid than that of the group with ileostomy performed for ulcerative colitis. Ileostomy for polyposis presents a greater problem; but when we do a combined ileostomy and colectomy, the patient recovers much more quickly and is rehabilitated with far less effort. I should like to know just why such patients do so well. Two patients with ileostomy and colectomy have had pregnancies, with normal full-term deliveries; they have families and in all respects lead normal lives.

Dr. Henry J. Tumen: The colostomy patient usually has very little disturbance because of his fistula. Often, when presenting the idea to the patient, the physician apologizes and worries about the adjustment the patient will have to make. One seldom encounters a "dissatisfied customer." Patients handle these things well, not only physically but emotionally. I do not know why this is true of colostomy patients—perhaps because they have been relieved of their cancer and are assured of future well-being. Also, they are often older people. Colostomy patients fundamentally do not have the emotional disturbance or background that ileostomy patients have, most of whom have ulcerative colitis.

It is now known that ulcerative colitis occurs mostly in persons who have emotional disturbances—they are likely to be immature, hostile, and disturbed in many respects—but the nature of the organic disease has not been clearly worked out.

Dr. Margolin says these people eroticize their fistulas. If he means they get some physical pleasure from them, possibly so. If he means there is sexualization of these fistulas, that may be true of some patients, but I do not see how it can be determined. I should like to know whether good results from ileostomy can always be forecast. This paper does demonstrate that patients with fistulas utilize their fistulas in some way. Whether it is true in all cases is something that should be studied.

Dr. Vincent P. Mahoney: This paper was not the usual discussion of what a particular emotion did to a particular viscus. The multiplicity of emotional factors acting on a viscus is a problem encountered clinically very often. I noted an absence of specific conflict that one hears so much about. It is rather discomforting to go back to the office and see patients who have had similar conflicts and who do not have the same reaction.

If such a patient has a biologic problem, he has to adapt to it and does so by using certain emotional mechanisms. One sees a great many people who have colostomy for a neoplasm of the bowel and who do not present a problem like this. It calls to my mind a number of questions: Can the patient regard the colostomy simply as a colostomy? Are there patients who do that, or do all of them have some minimal displacement? Are all these patients persons who were disturbed before surgery? Would such a patient have much more difficulty in making an adjustment? I hope that we by means of research shall be able to predict whether a patient who must have a colostomy will do well.

One wonders, too, whether the interest of the therapist might tend to fix the interest of the patient on the displacement, that is, whether he might not therefore be more inclined to eroticize. Many patients have a colostomy fistula and no analyst.

Dr. Sydney G. Margolin, New York: I do not regard these patients as unusual types of persons who have lesions. Except for the boy with the ileostomy, all made adequate spontaneous adjustments. They were not under psychotherapy for failure to deal with their lesions. They simply were patients who presented an opportunity for examining an organ, and we had to know what the organ meant to the patient in order to know about something we were investigating. We were able to demonstrate that an opening into a patient's body does influence the data. You have answered the question yourself when you say that most patients with a colostomy fistula seem to make peace with their fistula. Why does the physician, in advance, fear the results of the colostomy, while the patient seems to know better? I have attempted to report the results of an investigation on what goes on in a patient when he makes peace with a new opening in his body. "Erotization" is a term I use because I know of no other term for the emotional satisfaction of the patient.

As to the interest of the investigator in the lesion as a factor in erotization, that is a very important point. Only by knowing what the lesion means to the patient can one find out what prevents him from adapting to his lesion.

The question is raised as to whether the amount of psychological disturbance in a patient has any relation to the degree of adaptation to the lesion. I know of several patients in whom the severity of the disease, the psychological illness, and the reaction to the lesion were related, and the patient's disturbance had to do with his attitude toward the erotic function that had to be displaced and substituted. The patients would come around with all kinds of phantasies, and then they would say, "This is indecent."

If you know enough about a particular patient, you can predict what his reaction to a body opening will be. We examine the patient before he is operated on and tell the surgeon, "This patient will be depressed," or "He will react in this way," or I tell the surgeon that the operation should be deferred as long as possible until we can make some adjustment for the patient. The surgeons in our hospital respect the psychiatrist's comments on the various patients. Results can be predictable, although so far as colostomy or ileostomy is concerned, I could not say in particular. We have an "—ostomy club" in our community where such patients can get together.

How many of your patients invented pet names for their colostomy fistulas?

Dr. Howard D. Trimpi: A small number; probably about 5%.

Dr. Sydney G. Margolin, New York: I should say that you have not asked your patients about this point.

Dr. Howard D. Trimpi: I have often asked them; I am very much concerned with their personality and opinions of their colostomy fistulas. If they do have a pet name, they lose no time in acquainting one with it. Often, they deny it.

Dr. Sydney G. Margolin, New York: Every one has pet names for certain parts of the body, especially as children. When we grow older and become embarrassed, it is remarkable

how the pet names come back. The colostomy patient has reacted in the same way as he did many years before, when as a little girl or boy he gave pet names to parts of the body with pleasurable associations.

I am interested in Dr. Trimpi's point as to the difference between a patient with ileostomy for polyposis and one with ileostomy for ileitis. I gather that one is greatly troubled by adaptation to the new lesion, and the other is not.

Dr. HOWARD D. TRIMPI: The patient with an ileostomy for polyposis is generally much easier to rehabilitate than the patient with the operation for ulcerative colitis. That is partly due to the decided electrolyte difference.

Dr. SYDNEY G. MARGOLIN, New York: Which is the healthier patient?

Dr. HOWARD D. TRIMPI: The majority of patients with ulcerative colitis have an immature personality. If one can draw any conclusions about these patients, it is that they have some degree of immaturity in their personality. They are petulant, and one has to give in and use one's powers of persuasion oftener than with patients undergoing ileostomy for polyposis.

Obituaries

KAREN HORNEY, M.D.
1885-1952

Karen Horney, dean and one of the founders of the American Institute for Psychoanalysis, died in New York on Dec. 4, 1952, at the age of 67. She was born in Hamburg, Germany, on Sept. 16, 1885, the daughter of a Norwegian sea captain and a Dutch mother. Her eager interest in life and in the varieties of human experience began with many childhood voyages with her father and continued throughout her life, to include visits to many lands—Mexico, Central and South America, the countries of Europe, the islands of the Pacific, and Japan.

In 1909 she married Oscar Horney, a Berlin lawyer, and was widowed in 1925. Three daughters, Miss Brigitte Horney, of New York; Dr. Marianne von Eckhardt, of Bethesda, Md., and Mrs. Renate Crevenna, of Mexico, survive her. She studied at the University of Berlin, receiving her medical degree in 1913. From 1914 to 1918 she studied psychiatry at Berlin-Lankwitz, Germany, and from 1918 to 1932 she taught at the Institute for Psychoanalysis at Berlin. Dr. Horney came to the United States in 1932 and for two years was associate director of the Institute for Psychoanalysis, Chicago. She then came to New York, to begin the most creative and productive period of her life. Until 1941 she taught at the New York Psychoanalytic Institute and then became one of the founders of the Association for the Advancement of Psychoanalysis and the American Institute for Psychoanalysis.

In her book "New Ways In Psychoanalysis" (New York, W. W. Norton & Company, Inc., 1939) is one of the clues to this remarkable productivity in the last 15 years of her life. She said, "The greater freedom from dogmatic beliefs which I found in this country alleviated the obligation of taking psychoanalytical theories for granted, and gave me the courage to proceed along lines which I considered right." Trained, practicing, and teaching in terms of the Freudian theories, she none the less believed that "deference for Freud's gigantic achievements should show itself in building on the foundations that he has laid, and that in this way we can help to fulfill the possibilities which psychoanalysis has for the future, as a theory as well as a therapy" (The Neurotic Personality of Our Time, New York, W. W. Norton & Company, Inc., 1937). Her early investigations focused on the emotional problems of women. She saw with increasing clarity the deeper meaning of cultural influences and the limited value of a biological and sex-centered approach to the understanding of neurosis and human nature.

In more than two dozen papers, five books, and many theoretical and technical courses that she taught, Karen Horney took her place as a leader in the history of psychoanalysis. The theory of neurosis and human growth which arose from her keen clinical sense, and from her deep interest in therapy and in people, is based on the belief that "man has the capacity as well as the desire to develop his potentialities and become a decent human being," and that "man can change and go on changing as long as he lives" (Our Inner Conflicts, New York, W. W. Norton & Company, Inc., 1945). Through her work we see man, not mechanistically, as the helpless consequence of instincts and social pressures, but as a purposing organism, wanting to grow toward realization of self. We see neuroses as a distorted development in the course of this striving, rather than as the repetition of infantile fixations. It is all in James Stephen's "Crock of Gold": "What the heart knows today, the mind will understand tomorrow." That was Karen Horney, and it is the measure of the loss the art and science of psychoanalysis has suffered by her death.   NORMAN KELMAN, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CONVERSION OF GLUCOSE TO AMINO ACIDS BY BRAIN AND LIVER OF THE NEW-BORN MOUSE.
R. J. WINZLER, K. MOLDAVE, M. E. RAFELSON JR. and H. E. PEARSON, J. Biol. Chem.
199:485, 1952.

The incorporation in vitro of radioactive carbon from uniformly labeled C^{14}-glucose into the individual protein-bound amino acids of adult mouse brain and of one-day-old mouse brain or liver has been compared with the incorporation in vivo of glucose into the protein-bound amino acids of one-day-old mouse brain, liver, or intestine. The metabolic behavior of one-day-old mouse brain, especially in the in vitro incubations, was found to be unique in that all the essential and nonessential amino acids except proline and threonine were significantly labeled. Radioactivity in the other systems was largely limited to aspartic acid, glutamic acid, alanine, serine, and glycine (aminoacetic acid). The data are indicative that in the one-day-old mouse brain degradation products of amino acids may be in metabolic equilibrium with intermediates derived from glucose. This could result in appearance of radioactive carbon from glucose in essential amino acids with no net synthesis of these amino acids. The results are, therefore, not necessarily at variance with the well-established concept of essential amino acids, but do emphasize the caution necessary in transferring interpretation from in vitro to in vivo experiments.

PAGE, Cleveland.

EFFECT OF DIET ON TISSUE CHOLINE OXIDASE. D. A. RICHERT and W. W. WESTERFELD,
J. Biol. Chem. **199**:829, 1952.

Weanling rats had about one-half the adult level of liver choline oxidase; a purified 21% casein diet containing riboflavin, thiamine, pyridoxine, pantothenate, nicotinic acid, and choline yielded normal adult levels in two to four weeks. A low-protein or a riboflavin-deficient diet gave low values, whereas a thiamine or pyridoxine deficiency had no effect. The addition of 0.1% iodinated casein to the diets fed weanling rats for four weeks consistently decreased the liver and kidney choline oxidase by about one-third, irrespective of the composition of the diet.

PAGE, Cleveland.

TIME COURSE OF LIPIDE LABELING IN THE INTACT MOUSE AND RAT. J. T. VAN BRUGGEN,
T. T. HUTCHENS, C. K. CLAYCOMB, and E. S. WEST, J. Biol. Chem. **200**:31, 1953.

The time course of lipid and carbon-dioxide labeling following a single intraperitoneal injection of a tracer amount of acetate-1-C^{14} is described. In mice, maximum incorporation into fatty acids and cholesterol fractions occurred within 30 minutes. No progressive change was seen up to eight hours. Rats showed maximum incorporations in fatty acid and cholesterol fractions of either total body lipids or of lipids of skin, liver, gut, carcass, and brain with spinal cord in less than 21 minutes. Significant changes from these maximum values during the subsequent four hours were not observed. No evidence was found for the presence of a rapidly metabolizing fatty-acid fraction in rat liver or in the total rat or mouse.

PAGE, Cleveland.

INFLUENCE OF THE ADRENAL CORTEX ON THE MOBILIZATION OF TISSUE PROTEIN. S.
ROBERTS, J. Biol. Chem. **200**:77, 1953.

The release of protein to a serum medium by rat liver and splenic tissue in vitro was increased by previous treatment of the animals with adrenal cortex extract or corticotropin. Adrenalectomy depressed the rate of protein release. The protein released by liver tissue possessed the electrophoretic mobility of serum α-globulin; that released by spleen was similar to serum

β-globulin. Disappearance of albumin from the serum medium was coincident with the addition of globulin. Evidence was obtained that the tissue proteins labilized by pituitary-adrenocortical stimulation may be utilized for accelerating liver regeneration in the partially hepatectomized rat. The increased repair of the liver as a result of administration of adrenal cortex extract or corticotropin in this preparation was characterized primarily by an increased deposition of liver protein. No increase in serum or urinary nonprotein nitrogen was observed under these conditions, but the usual decline in serum proteins occurring after partial removal of the liver was completely prevented by hormone treatment. The results indicate that the primary effect of the adrenocortical secretions on nitrogen metabolism involves an accelerated mobilization of protein. This action appears to be effected by a labilization of tissue protein and the resulting translocation of this protein to other sites in the body in the form of specific plasma proteins. The end-result of pituitary-adrenocortical activation in this respect may be local or systemic protein anabolism or catabolism, depending upon the tissue requirements for protein at the moment.

PAGE, Cleveland.

BIOSYNTHESIS OF SQUALENE. R. G. LANGDON and K. BLOCH, J. Biol. Chem. **200**:129, 1953.

In 1916 Tsujimoto isolated from shark liver oil a hydrocarbon having the empirical formula $C_{30}H_{50}$, which he named squalene. Later, Heilbron and co-workers established the structure of this hydrocarbon as that of a dihydrotriterpene. The compound has more recently been found to be of widespread occurrence. It has been reported to occur in yeast, palm oil, human dermoid cysts, and human sebum. However, it is not known whether squalene is synthesized by animals or whether its ultimate source is ingested plant material. When squalene is fed to rats, 5 to 10% of the administered hydrocarbon can be recovered from the tissues. It has been demonstrated that squalene is synthesized by the tissues of the rat. Both carbon atoms of acetic acid are utilized in this process. Squalene is a normal constituent of rat liver. It occurs in low concentrations and is regenerated at a rapid rate.

PAGE, Cleveland.

UTILIZATION OF SQUALENE IN THE BIOSYNTHESIS OF CHOLESTEROL. R. G. LANGDON and K. BLOCH, J. Biol. Chem. **200**:135, 1953.

C^{14}-squalene prepared biosynthetically from acetate is efficiently converted to cholesterol in the tissues of the mouse. The preparation of C^{14}-squalene and of deuterium-labeled squalene is described. These compounds, which are shown to be structural isomers of the natural-occurring hydrocarbon, are not utilized in steroid biosynthesis. The part played by squalene as an intermediate in cholesterol biosynthesis is discussed.

PAGE, Cleveland.

EFFECT OF ABLATION OF PRESTRIATE CORTEX ON AUDITORY-VISUAL ASSOCIATION IN MONKEY. E. V. EVARTS, J. Neurophysiol. **15**:191 (May) 1952.

This study was designed to determine the role of corticocortical connections between the striate area and the rest of the cortex in the performance of a task requiring response to both visual and auditory cues. Evarts found that extensive ablation of the prestriate area (Brodmann's area 18) in the monkey (Macacus mulatus) was without effect on either retention or postoperative learning of a conditional problem requiring the subject to select a red stimulus in the absence of sound and a green stimulus in the presence of the sound of a buzzer. The significance of this finding with regard to the behavioral role of corticocortical connections is discussed.

ALPERS, Philadelphia.

OBSERVATION ON THE MECHANISM OF EXPERIMENTAL CEREBELLAR SEIZURES. S. L. CLARK and J. W. WARD, J. Neurophysiol. **15**:221 (May) 1952.

When the cerebellum is stimulated in normal animals through concentric electrodes permanently implanted so that the animal can move freely without displacing them, a peculiar type of seizure is produced that involves the animal's musculature in a sequence, or "march," the pattern of which is partly determined by the region stimulated. In further attempts to analyze the mechanism of the response of the cerebellum to stimulation, and of those "cerebellar"

seizures following at times upon cerebral stimulation, Clark and Ward carried out certain operative procedures on the nervous system in a series of cats and observed the effects on the responses to cerebellar stimulation.

They found that cerebellar seizures from cerebellar stimulation occur in the absence of the motor area and most of the cerebral cortex. Although the pathways concerned with the muscular movements involved are not known, the seizures may occur in complete form after section of one basis pedunculi, a pyramid, the dorsal roots to an extremity, the vestibular apparatus, both eighth cranial nerves, or the upper three cervical nerves of both sides. The seizures may occur in complete form after partial splitting of the cerebellum, or in modified form; or they may be confined to the homolateral side after complete splitting of the cerebellum.

With simultaneous stimulation of the cerebral motor area and the cerebellum no evidence of inhibition of movements induced by the cerebral stimulation was seen, but there was some evidence of facilitation. The cerebral stimuli and associated movements, when brief, did not stop or obviously change the cerebellar effects. Since the sequence of movements throughout a seizure are paired and contrasted like the phases of stimulus and rebound, the authors suggest that this may represent a basic phenomenon in normal functioning of the cerebellum in its control of muscle synergy.

ALPERS, Philadelphia.

CORTICAL PROJECTION ZONE OF CHORDA TYMPANI NERVE IN CAT. H. D. PATTON and V. E. AMASSIAN, J. Neurophysiol. **15**:245 (May) 1952.

Patton and Amassian report attempts to determine the cortical location of taste in cats by mapping the zone electrically responsive to stimulation of the chorda tympani.

They found that the cortical response to single-shock excitation of the chorda tympani was a surface-positive wave of 50- to 100-μv. amplitude and 10- to 12-seconds latency. Responses were limited to a cortical area of 5 to 10 sq. mm. on the orbital surface of the hemisphere, superior to the rhinal fissure and rostral to the anterior ectosylvian fissure. Other cortical areas, including the insula, were unresponsive.

The receptive zone for the chorda tympani is rostral and lateral to the tactile receptive zone for the face but extensively overlaps the tactile representation of the tongue. The chorda tympani, like the tactile projection from the tongue, is bilaterally represented.

The authors discuss the implication of these findings with respect to cortical localization of taste.

ALPERS, Philadelphia.

NEUROPHYSIOLOGICAL STUDIES ON CEREBRAL CONCUSSION. R. B. AIRD, L. S. STRAIT, D. ZEALER, and M. HRENOFF, J. Neurosurg. **9**:331 (July) 1952.

Considerable neurophysiological evidence previously reported suggests that the permeability of nerve tissue and of blood-brain barrier is altered after cerebral concussion and that this may be associated with profound physiological changes and dysfunction, even though neuropathological findings are slight or absent. These experimental studies have suggested that cerebral injuries may produce three types of effects: (a) an alteration of the permeability of the entire blood-brain barrier after cerebral concussion, (b) a local modification of permeability, and (c) a local modification of the reactivity of the nerve tissue focally injured.

The neurophysiological studies reported in the present investigation, in which the authors used a modified spectrochemical technique for following the distribution of cocaine, were performed on cats under control conditions and after cerebral concussion. The object of these experiments was to determine whether or not alterations in the concentration of cocaine occurred in the central nervous system after cerebral concussion which might reflect permeability effects in the blood-brain barrier of possible etiologic significance in postconcussional head conditions. Significant increases in the concentration of cocaine were found in the cerebral cortex, indicating that cerebral concussion increases the permeability of the blood-brain barrier.

Electroencephalographic studies indicated that approximately 80% of the cats showed cerebral dysrhythmia three days after cerebral concussion. From these observations arises the interesting possibility that these persistent postconcussional phenomena, e. g., the increased permeability of the blood-brain barrier and cerebral dysrhythmia, may correlate better with the clinical symptoms seen after concussion than the transient alteration of permeability observed in cortical

tissue by Spiegel after concussion. Aird and his colleagues propose the theory that the maximal effect of a concussive blow occurs at the point of contact between the cellular masses of the brain and such relatively fixed structures as the supporting vascular tree of the brain. It is postulated that disrupting effects at these points of contact might produce alteration of vascular permeability and secondary neurophysiological changes affecting cerebral metabolism, and that in severer cerebral trauma perivascular pathology might be produced resulting in irreversible changes of a degenerative character.

Similar studies were carried out after preliminary injections of trypan red. Trypan red appears to counteract both the increase in permeability of the blood-brain barrier and the cerebral dysrhythmia associated with cerebral concussion. Preliminary clinical studies, being conducted at present by the authors, suggest that trypan red and other agents which have a corresponding effect on the blood-brain barrier may have a beneficial effect on the postconcussional state.

ALPERS, Philadelphia.

ON THE PHENOMENON OF PARACUSIS WILLISI. L. HALPERN, Harefuah **43**:123 (Nov.) 1952.

In 1672 Willis observed in his book "De anima brutorum" that deaf people sometimes hear better in the presence of noise. There has as yet been no satisfactory explanation of this phenomenon. Hearing and vibration resemble each other and seem to be functionally related. They both pick and perceive rhythmic oscillation. It is also noted that the fish keeps in contact with its environment by perceiving vibrations in the water. Deaf people can be aware of passing vehicles or of the noise of a pounding hammer due to transmitted vibratory sensation. Vibration apparently has an effect on the auditory threshold and improves hearing ability. Usually hearing and vibration together facilitate perception of the outer world.   SAVITSKY, New York.

Diseases of the Brain

CAT-SCRATCH FEVER ENCEPHALITIS. H. STEVENS, A. M. A. Am. J. Dis. Child. **84**:218 (Aug.) 1952.

The author reports the first case of encephalitis associated with cat-scratch fever. In all previous reports the benign and self-limiting nature of the disease has been emphasized.

The patient, first seen in 1949, was a white boy of 13 with a history of having received a cat scratch, at the site of which a local indolent ulcer had developed, with enlargement and suppuration of the local axillary lymph nodes. Intensive study of the pus revealed no organisms. A transient rash developed; this failed to respond to penicillin but did improve with aureomycin. One week after the initial symptoms of headache and fever he showed signs of encephalitis, with severe and multiple convulsions, positive neurological signs, including nuchal rigidity, and an abnormal electroencephalogram. None of the studies made at that time gave any evidence as to the cause of the encephalitis.

After fever had subsided with aureomycin therapy and the patient had been discharged, the axillary lymph nodes suppurated and drained, with gradual healing after three months. The boy showed some behavior difficulties for a time, but these were completely resolved. A second electroencephalogram, made almost two years later, was still slightly abnormal; but there was no focus of abnormal activity, and he had no convulsions after the acute illness.

As a consequence of the recent literature on cat-scratch fever, a retrospective diagnosis was made two and one-half years after the illness. Even after this long internal skin tests gave a severe cutaneous reaction, and the serum complement fixation test was strongly positive, suggesting an unusually heavy inoculation.

Stevens again emphasizes the possibility of the encephalitis occurring as a complication in cat-scratch fever.   ALPERS, Philadelphia.

MEASLES ENCEPHALITIS: A FOLLOW-UP STUDY ON SIXTEEN PATIENTS. E. MEYER and R. K. BYERS, A. M. A. Am. J. Dis. Child. **84**:543 (Nov.) 1952.

Children who had had measles encephalitis were studied for 14 months to 6 years. The authors emphasize the psychologic examinations by interview (including family) and appropriate

tests. Since difficulties in mental function were not characterized by reversion to younger mental levels but, rather, represented perversions, they were not easily scorable and needed to be interpreted qualitatively or on a percentile basis. It appeared that abnormalities definable by these tests were based on structural disease. There was a close correlation between the length or the acute illness and the psychologic outcome; patients with short courses had fair to excellent restitution of psychologic function, regardless of age. However, though these children appeared clinically recovered on discharge, some disabilities were detectable by special test procedures up to a year later. More obvious disabilities were observed in the children who had prolonged illnesses. On discharge, almost all the latter were confused, flighty, and unable to sustain attention, and only for brief periods could they reactivate previously learned mental patterns. The psychologic difficulties seemed largely dominated by difficulties in attention. Defects in perceptual-spatial organization were exhibited and made acquisition of primary school techniques very difficult for those who had not previously been schooled. These defects may have been secondary to attention disorders. About one-half the severely ill children exhibited relative deterioration in intelligence quotients through the years, though it was sometimes three years before the intelligence-quotient adequately described this. In these children the mental age did not advance with the chronologic age, and the acquisition of new intellectual syntheses was difficult. The older children showed less deterioration, and this seemed to be the result of the greater experience on which to build; the younger ones had to attempt to acquire elementary adaptation with defective tools.

The personality changes were clearly related to observed psychologic disabilities. The patient's relation to the environment was distorted by difficulties in perception and attention. Reactions were impulsive, and the patients were frequently frustrated. Environmental flexibility had a bearing on behavior. In the less severely ill, this adjustment was easier than in children whose convalescence was protracted. It seemed that personality changes did not arise as completely radical ones but appeared as overemphasis of traits already present. Environmental adjustments did not seem to influence basically the pathologic changes underlying the intellectual deficits.

SIEKERT, Rochester, Minn.

INCORPORATION OF LABELED METHIONINE INTO PROTEIN BY PITUITARY TISSUE. J. B. MELCHIOR and M. N. HALIKIS, J. Biol. Chem. **199**:773, 1952.

Measurements were made of the ability of pituitary tissue to incorporate a labeled amino acid into protein in vitro. The method described permits measurements with the single rat pituitary. Pituitary tissue was found to be much more active in the incorporation of the labeled amino acid than was liver. The activity was significantly greater in young animals. After the first two weeks of life the activity remained relatively constant, with a tendency to decrease in the older rats. No significant difference was found during the phases of the estrous cycle or during pregnancy. The male gland had the same activity per gram as the gland of the normal adult female; because of the smaller size of the animal, the total activity in the male was significantly less than that in the female. During lactation a significant decrease in the ability of the gland to label protein was observed.

PAGE, Cleveland.

PROJECTION OF CORTICAL AREA TO BRAIN STEM IN MONKEY. E. W. PETERSON, and D. S. BICKERS, J. Neurophysiol. **15**:87 (March) 1952.

It has been shown that after section of the pyramids electrical stimulation of Brodmann's cortical Area 6 elicits movement in somatic musculature. This communication describes an attempt to elucidate the first neurons of the descending pathway concerned.

The authors found that after strychnine activation Area 6 can be shown to project ipsilaterally to the subthalamic nucleus, the substantia nigra, the tegmentum of the midbrain and pons, the red nucleus, and the central gray matter.

The tegmental regions concerned are ventral and dorsolateral portions in the midbrains and pons. These connnections must subserve the motor activity, which can be demonstrated on stimulation of Area 6 after pyramidal section.

ALPERS, Philadelphia.

The Cerebellar Angioreticulomas. H. Olivecrona, J. Neurosurg. 9:317 (July) 1952.

Olivecrona reports on a series of 4,101 cases of verified brain tumors, 70% of which were cases of cerebellar angioreticuloma. In adults this neoplasm occupies fourth place among the tumors of the posterior fossa, occurring with practically the same frequency as the meningiomas, but less frequently than the gliomas and neurinomas.

Cyst formation was found to be less frequent than is generally thought, and almost one-fifth the tumors observed were entirely solid. In 5 cases the tumor was localized to the region of the fourth ventricle; in 9, to the vermis, and in the remaining 56, to a cerebellar hemisphere. In one case angiomatosis retina was observed. Three families were observed in which two or more members of the family had angioreticuloma.

Increased intracranial pressure is the most important, and also the first, sign in most cases. Headache is usually the initial symptom, vertigo may appear simultaneously or soon after headache, and vomiting is frequently an early symptom. Cerebellar symptoms were found in most cases, but were often late in appearance. Of the cerebellar signs, only nystagmus is of greater localizing value than intracranial tension in those cases in which signs of the latter have been present for some time. Cranial nerve paralyses, especially facial weakness and sensory disturbances in the trigeminal field, were observed in several cases.

Air studies were carried out in all but three cases. The author points out that lumbar encephalography is contraindicated when a cerebellar angioma is suspected. Air injection after the ventricles have been tapped is by far the safest, and also the most reliable, method for establishing the diagnosis of cerebellar angioma. He emphasizes the necessity of following ventriculography with immediate operation; otherwise the procedure is extremely dangerous. A specific indication for vertebral angiography arises in cases of familial occurrence of angioma. Multiple tumors are frequently present in these cases, and angiograms may disclose the presence and location of multiple tumors.

In six cases death occurred before operation. In one case the tumor was considered inoperable and decompression only was performed, with an early fatality. In 63 cases the tumor was completely removed, with 10 fatalities. For 64 cases, therefore, the mortality was 17.2%. Tumors in the floor of the fourth ventricle carried a very high mortality, the operation having terminated fatally in two of five such cases.

Of the survivors, six died later of intercurrent disease. Five of the survivors are invalids—3 because of blindness, 1 because of mental impairment, and 1 because of cerebellar incoordination. The remaining 42 patients are well and able to work.   Alpers, Philadelphia.

Benign Arachnoid Cyst of the Posterior Fossa. W. V. Trowbridge and J. D. French, J. Neurosurg. 9:398 (July) 1952.

Benign monolocular cysts of the arachnoid in the posterior fossa are rare. Trowbridge and French briefly summarize five cases found in the literature and present a sixth, that of a man aged 25.

Such a cyst, acting as a space-consuming lesion in the midline of the posterior fossa, precipitates symptoms primarily through obstruction of the fourth ventricle and interference with the circulation of the cerebrospinal fluid. Cases of this cyst are characterized by signs of intermittent, severe intracranial hypertension and a paucity of localizing signs. Although the series of cases is small, it is pointed out that the age distribution is in the third and fourth decades only. It may be suggested that the wall of the cyst is actively secreting, at a very slow rate, and that the cyst might thus slowly enlarge over the years to a point at which intermittent obstruction to the cerebrospinal-fluid pathway occurs.

Etiologic factors suggested in the causation of these cysts are trauma, inflammation, and a congenital factor. From the evidence in their case, Trowbridge and French favor the congenital origin.

In all cases, distress was immediately and, to all appearances, permanently relieved by removal of the cyst. Although in none of these cases was the lesion correctly diagnosed, or even suspected, prior to operation, the cyst should be counted among the favorable operative lesions of the posterior fossa.   Alpers, Philadelphia.

CHRONIC NEUROLOGICAL DISEASE AS A POSSIBLE FORM OF LEAD POISONING. E. J. BUTLER. J. Neurol., Neurosurg. & Psychiat. **15**:119 (May) 1952.

It has long been known that the clinical manifestations of lesions in the nervous system produced by lead are diverse and may simulate the symptoms of various chronic neurological diseases. Early workers thought that lead might be an etiologic agent in such disease—for example, multiple sclerosis.

With improved analytical methods for the determination of lead, Butler studied four groups of patients: (1) 26 patients with multiple sclerosis and 5 patients probably affected with the disease; (2) 56 patients with other chronic neurological diseases, some of which, e. g., spastic paraplegia and peripheral neuritis, may be simulated by lead poisoning; (3) 7 patients with slight nonspecific symptoms, of whom 6 had experienced an occupational exposure to lead, and (4) 4 industrial workers with lead poisoning.

It was found that patients with multiple sclerosis showed no significant difference from those with other chronic neurological disease as regards their urinary excretion of lead and its concentration in the blood, cerebrospinal fluid, and tibial cortex, which in all patients was within the normal limits. For comparison, the patients with confirmed lead poisoning showed that an abnormally high urinary excretion of lead and coproporphyrin is maintained long after clinical remission and the disappearance of hematologic changes. The coproporphyrin excretion in the two groups of neurological patients was not significantly different, and with a few exceptions was within the normal range.

The administration of dimercaprol to neurological patients by injection consistently produced an increase in urinary lead excretion. This response in terms of increased lead excretion bore no apparent relation to the disease studied, nor did its magnitude indicate the presence of abnormal amounts of lead in the circulation and soft tissue. The lead content of necropsy samples of tissue, including the brain and spinal cord, obtained in cases in which the diagnosis of multiple sclerosis was confirmed histologically showed that lead was not responsible for the lesion in these cases and that there had been no mobilization of lead from the skeleton.

These studies do not support the view that lead plays a part in the etiology of multiple sclerosis and certain other chronic diseases of the nervous system. ALPERS, Philadelphia.

EOSINOPHILIC GRANULOMA. MARSHAK, Harefuah **43**:173 (Dec.) 1952.

A 5-year-old boy was admitted to a hospital Jan. 8, 1952. Six weeks before admission he began to complain of pain in the region of the bridge of his nose. A short time afterward a swelling appeared in this region and remained about a week. It reappeared after four weeks. At the same time a swelling was noted in the region of the vertex of the skull, near the region of the anterior fontanel. The general condition of the child was good; there was no febrile rise. Upon his admission a small swelling was found near the bridge of the nose. The edges of the swelling were not well delimited. A defect in the bone could be felt in the center of the swelling. Another swelling was found in the region of the anterior fontanel; it was a little larger. Roentgenograms showed defects in the skull bones, about 2 cm. in diameter, in the region of swelling. No bony defects were found in other parts of the skeleton. The blood cell count showed 2.3% eosinophiles. Operation, on Jan. 17, 1952, showed an eosinophilic granuloma at each site; the destruction of bone in the region of the anterior fontanel extended to the dura. Histologic study of the curetted bone was reported as revealing an eosinophilic granuloma. Some histiocytes were noted, in addition to the eosinophilic polymorphonuclear leucocytes. Both these lesions disappeared with x-ray therapy. On March 4 a swelling and bone defect were noted in the region of the left mastoid. This bone defect cleared up completely with x-ray therapy alone. Follow-up examination seven months after the child was first seen showed complete recovery. Since Jaffe and Lichtenstein described this lesion in 1940, there has been considerable difference of opinion as to whether it is a distinct clinical entity or whether it is related to Hand-Christian-Schüller disease or Letterer-Siwe disease. The author does not express his own opinion. SAVITSKY, New York.

Peripheral and Cranial Nerves

THE JUGULAR FORAMEN SYNDROME. J. H. FONT, A. M. A. Arch. Otolaryng. **56**:134 (Aug.) 1952.

Laryngeal paralysis may occur in association with other motor paralysis and with paresthesias and anesthesias. There are two major classes of paralysis of this type: (1) those in which recovery does not take place and (2) those of a temporary nature. The author gives an anatomicophysiologic review of the jugular foramen and the nerves traversing it and reviews the literature concerning the numerous etiologic factors in the jugular foramen syndrome. He draws particular attention to a summary by Engström and Wohlfart which focuses attention on the possibility that the paralysis may sometimes be a local manifestation of a viral infection characterized primarily by herpetic eruptions. These workers reported five such cases.

Font here presents two new cases in which the association of the herpetic eruption, the generalized illness, and the onset of paralysis were so close that the assumption of a viral origin seems justified. Both patients recovered.

A detailed analysis of the literature dealing with these paralyses shows that in many of the reported cases herpetic lesions have been an unemphasized component.

The author proposes that in the absence of obvious lesions in neighboring structures, and when the paralysis is accompanied by general manifestations, the syndrome of the jugular foramen be studied from the point of view of a possible viral origin.

ALPERS, Philadelphia.

TRIGEMINAL NEURALGIA. M. M. PEET and R. C. SCHNEIDER, J. Neurosurg. **9**:367 (July) 1952.

The authors report the data on 689 patients with trigeminal neuralgia who were examined over a 10-year period. The data concern age and sex incidence, side of involvement, duration of symptoms, division involved, trigger zones, preoperative complications, operations, immediate complications, postoperative problems, and number of deaths. Follow-up study was accomplished by questionnaire, to which 65% of the patients replied.

The series comprised 553 patients who had trigeminal rhizotomy, 49 who had received only alcohol injections, and 87 others for whom the diagnosis was made but who were not treated.

From this survey, Peet and Schneider conclude that trigeminal rhizotomy is a much more satisfactory procedure than alcohol injection in the average case of trigeminal neuralgia, for there was complete relief of tic pain in all but 5.4% of the patients treated surgically. Alcohol injection, in this series, relieved only 15.2% of the patients for longer than one year.

Unpleasant postoperative symptoms, such as crawling and burning paresthesias, occurred in a fairly high percentage of the rhizotomy patients, approximating the incidence of these symptoms after alcohol injection. However, the great majority of patients are so relieved because of the cessation of their severe tic pain that they find these discomforts endurable. The authors believe that proper forewarning of the patients about such possible postoperative symptoms is important and rewarding.

The operative mortality rate in the entire series was 1.6%. The procedures were carried out by 14 surgeons and 34% of the patients were over 65.

In only 6.5% of the patients who underwent operation did facial paralysis occur, and in no known instance in this series was it permanent.

ALPERS, Philadelphia.

AN UNUSUAL CASE OF UNILATERAL EIGHTH NERVE TUMOR. V. H. MARK and W. H. SWEET, J. Neurosurg. **9**:395 (July) 1952.

The occurrence in the younger age group of bilateral acoustic tumor, or acoustic tumor associated with Recklinghausen's disease, or neurofibromatosis, is well known. Cushing stated that "a patient under 20 with a cerebellopontile-angle syndrome in all likelihood has a lesion other than an acoustic tumor."

The case of unilateral acoustic nerve tumor presented by the authors proves to be an exception to that rule, for the age of onset was 6 years and the neuroma was removed and the diagnosis

verified histologically when the boy was 8½ years old. Furthermore, the patient showed none of the associated stigmas of Recklinghausen's disease, as determined either by physical examination or from the family history. Other unusual features of this case include normal spinal fluid protein and massive destruction of the pyramid of the involved petrous bone.

ALPERS, Philadelphia.

COMPRESSIVE LESIONS OF THE EXTERNAL POPLITEAL (COMMON PERONEAL) NERVE. H. GARLAND and D. MOORHOUSE, Brit. M. J. **2**:1373 (Dec. 27) 1952.

From a study of 20 cases of uncomplicated external popliteal paralysis, Garland and Moorhouse are convinced that the condition always arises from compression of the nerve as it winds around the neck of the fibula. They were usually able to elicit a history of kneeling, bandaging, crossing the legs while sitting, lying on a hard surface, or wearing of knee pads. The fact that their cases were from such scattered sources led them to the belief that this type of paralysis is not uncommon. It is of sudden onset and painless. In their cases the incidence of damage was much greater in the motor than in the sensory fibers. Complete recovery occurred in 13 of the 20 cases and partial recovery in the rest. A brief report of the 20 cases is included.

ECHOLS, New Orleans.

DIABETIC ARTHROPATHY: NEUROGENIC ARTHROPATHY IN DIABETIC PATIENTS. I. BLUMENFELD and C. A. CAMPOS, Prensa méd. argent. **38**:2722 (Oct. 19) 1951.

Jordan first reported a case of neurogenic arthropathy in a diabetic in 1936 (*Arch. Int. Med.* **57**:307, 1936). To date, 29 cases have been reported. In most cases the arthropathy involved the foot. Amputation became necessary in only one case other than the authors'. The present case is the first to be published in Spanish. A woman aged 55 had diabetes mellitus of 12 years' duration and had complained of loss of weight and pains in the lower limbs for two years. In June, 1949, she began to complain of pain in the left instep. The inner side of the left foot became swollen and bluish. Ulceration did not appear. The dorsalis pedis pulse was the same on the two sides. X-ray examination showed destructive lesions in the bones on the inner side of the left foot. In June, 1950, biopsy of tissues at the affected site showed newformed bone and cartilage and a chronic inflammatory reaction. In July, 1950, the ankle jerk on the affected side was found to be diminished. There were marked sensory loss, involving especially pain and temperature perception, and diminution of pain and temperature sense on the outer side of the right foot. Spinal fluid studies during September, 1950, showed absence of flocculation, negative serologic reaction, 2 to 3 lymphocytes per cubic millimeter, and a total protein content of 40 mg. per 100 cc. Vibration sense was diminished in the left lower limb, and there was heel-to-knee ataxia on the left. A fistula finally appeared, and the left foot had to be amputated on Nov. 14, 1950. Pathologic examination showed diminution of the number of fibers in the anterior tibial nerve with increase of intrafascicular connective tissue. There were small areas of infiltration with round cells. The anterior tibial artery showed arteriosclerosis.

SAVITSKY, New York.

Congenital Anomalies

CONGENITAL TOXOPLASMOSIS OCCURRING IN IDENTICAL TWINS. W. F. MURPHY and J. L. FLANNERY, A. M. A. Am. J. Dis. Child. **84**:223 (Aug.) 1952.

Toxoplasmosis occurring in a pair of identical twins is presented. Clinical evidence of the disease was manifested by convulsive disorders, esotropia, and nystagmus. Funduscopic examination revealed extensive chorioretinitis in each case. Serological evidence of the disease was provided by positive complement fixation and high dilution titers in the dye test for each twin and for the mother. In neither twin was there any evidence of intracerebral deposits of calcium.

Two younger boy siblings born to the parents of the twins have shown no clinical or serological evidence of toxoplasmosis.

ALPERS, Philadelphia.

News and Comment

The Social-Psychological Therapy of Epilepsy

WILLIAM G. LENNOX and CHARLES H. MARKHAM, Boston

Discussion to be opened by H. HOUSTON MERRITT, New York, and EPHRAIM ROSEMAN, Louisville, Ky.

Cerebral Complications Associated with Pregnancy

BENJAMIN BOSHES and JUANITA G. McBEATH, Chicago

Discussion to be opened by E. D. FRIEDMAN and THEODORE J. C. VON STORCH, New York

Antispasmodic Compound 08958 in the Treatment of Parkinsonism

KENNETH R. MAGEE and RUSSELL N. DeJONG, Ann Arbor, Mich.

Discussion to be opened by LEWIS J. DOSHAY, New York, and ROBERT S. SCHWAB, Boston

Observations on the Course and Management of Myasthenia Gravis

DAVID GROB and A. McGEHEE HARVEY, Baltimore

Discussion to be opened by ROLAND P. MACKAY, Chicago, and HENRY R. VIETS, Boston

Thursday, June 4—2 p. m.

The Pharmacological Treatment of the Aged Hospitalized in an Institution for the Mentally Ill SOL LEVY, Medical Lake, Wash.

Discussion to be opened by HOLLIS E. CLOW, White Plains, N. Y.

The Distribution, Form, and Extent of Psychiatric Consultation Services in the United States

DANIEL BLAIN, Washington, D. C., and R. FINLEY GAYLE JR., Richmond, Va.

Discussion to be opened by FRANCIS J. GERTY, Chicago, LEO H. BARTEMEIER, Detroit, and C. N. BAGANZ, Lyons, N. J.

The Alleviation of Emotional Problems in Multiple Sclerosis by Group Psychotherapy ROBERT H. BARNES, EWALD W. BUSSE, and HAROLD DINKEN, Denver

Discussion to be opened by FRANKLIN G. EBAUGH, Denver, and WILFRED C. HULSE, New York

Prognosis in Psychiatry: The Results of Psychiatric Treatment

KENNETH E. APPEL, J. MARTIN MYERS, and ALBERT E. SCHEFLEN, Philadelphia

Discussion to be opened by LOTHAR B. KALINOWSKY and NOLAN D. C. LEWIS, New York

Psychotherapeutic Reeducation HARDIN M. RITCHEY, New Canaan, Conn.

Discussion to be opened by GEORGE N. RAINES and ZIGMOND M. LEBENSOHN, Washington, D. C.

Anxiety and Depressive States Treated with Isonicotinyl Hydrazide

HARRY M. SALZER and MAX L. LURIE, Cincinnati

Discussion to be opened by FRANCIS J. BRACELAND, Hartford, Conn., and FRANK H. LUTON, Nashville, Tenn.

DR. WARTENBERG AND DR. PUTNAM ELECTED CORRESPONDING MEMBERS OF RIO DE JANEIRO SOCIETY OF NEUROLOGY

Dr. Robert Wartenberg, clinical professor of neurology, University of California Hospital, and Dr. Tracy Putnam, Los Angeles, have been elected corresponding members of the Rio de Janeiro Society of Neurology.

RESIDENCIES IN PSYCHIATRY, VETERANS ADMINISTRATION HOSPITAL, LYONS, N. J.

The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training can commence at any time, and the program consists of lectures, conferences, and seminars, under the direction of the department of psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals in the adjacent area. There is, in addition, a series of extensive guest lecturers, as well as an annual institute at the hospital.

Books

Méthodes biologiques en clinique psychiatrique. By Jean Delay. Price, 2000 Fr. francs. Pp. 536, with illustrations. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 6e, 1950.

This book is the most extensive single treatise on the biological methods used both in the diagnosis and in the treatment of mental illness. Its author is the research professor of psychiatry of the University of Paris and chief of the famed Hôpital Sainte-Anne. Its hard core is the collection of papers written by the author himself. It consists of chapters on encephalographic methods (electroencephalography and pneumoencephalography, the latter both for diagnostic and for therapeutic purposes), on shock treatment and psychosurgery, and, finally, on psychochemistry (humoral and endocrine psychoses, chemotherapy, and pharmacodynamic explorations). The methods, discussed and beautifully illustrated by the sort of detailed case histories in which the Gallic writers excel, cover everything known in this country, and more. It is of special interest that air injection is widely used in France as a therapeutic method not only in frankly endocrine disorders, but also in the manic-depressive states. The chapter on organic psychoses indicates unusual alertness and diagnostic ingenuity in tracking down the etiology, which is sorely missed in countries where diagnostic orientation is predominantly nonbiological. The author's interpretative guide is the theory on psychic integration, as set forth by Jackson in his Croonian Lectures. Single accurate case observations, rather than large-scale statistical studies, are the basis of this book, which is written succinctly, and illustrated exactly, in beautiful French prose.

Schedule of Rates

	Hotel	Single Bedrooms	Double or Twin Bedrooms
31.	Abbey, 151 West 51st Street.......	6.00	8.50-10.00
32.	Ambassador, Park Ave. & 51st St.	11.00-15.00	14.00-18.00
58.	Astor, Broadway & 44th St.......	$ 7.00-18.00	$11.00-15.00
8.	Barbizon (For Women) 140 East 63rd St............................	4.75- 5.50	8.00- 8.50
12.	Barbizon-Plaza, 101 West 58th St.	6.50- 8.50	11.00-14.50
47.	Barclay, 111 East 48th St.........	Suites only	
62.	Beaux Arts, 310 E. 44th St.......	6.50- 8.50	8.50-12.00
43.	Beekman Tower, First Ave. & 49th St.	6.00- 8.00	7.00-12.50
1.	Bretton Hall, Broadway & 86th St.	4.00- 6.00	6.00- 7.00
45.	Bristol, 129 West 48th St.........	....	7.00- 8.50
46.	Chatham, Vanderbilt Ave. & 48th St.	6.50-11.00	14.00-16.00
65.	Claridge, Broadway & 44th St.....	6.00- 8.00	8.00-11.00
70.	Commodore, Lexington Ave. & 42nd St.	6.50- 9.50	10.50-14.00
64.	Dixie, 250 West 43rd St...........	5.00- 6.00	8.00- 9.50
11.	Essex House, 160 Central Park South	8.00-13.00	11.00-17.00
80.	Governor Clinton, Seventh Ave. & 31st St.	6.00- 7.50	8.50-12.00
83.	Gramercy Park, Lexington Ave. & 21st St.	5.00- 9.00	7.00-12.00
19.	Great Northern, 118 West 57th St.	6.00- 7.00	8.00-10.00
84.	Grosvenor, 35 Fifth Ave...........	7.00- 9.00	10.00-12.50
18.	Henry Hudson, 353 West 57th St..	5.00- 7.00	8.00-12.00
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86.	Madison, 15 E. 58th St............	6.50- 8.50	8.50-12.00
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55.	Piccadilly, 227 West 45th St......	6.00- 7.00	8.00-10.00
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49.	President, 234 West 48th St.......	5.00- 6.00	6.00- 8.00
82.	Prince George, 14 East 28th St....	5.00- 8.00	7.50-10.50
13.	St. Moritz, 50 Central Park South	Suites only	
15.	Savoy Plaza, Fifth Ave. & 58th St.	11.00-16.00	15.00-20.00
73.	Shelburne, Lexington Ave. & 37th St.	8.00-10.00	10.00-14.00
48.	Shelton, Lexington Ave. & 49th St.	6.00-11.00	8.00-14.00
78.	Statler, Woman's Auxiliary Hdqtrs. Seventh Ave. & 33rd St..........	6.00-10.50	9.00-17.00
25.	Sutton, 330 East 56th St..........	4.50	
35.	Taft, Seventh Ave. & 50th St......	4.75- 8.75	9.50-12.50
77.	Vanderbilt, Park Ave. & 34th St..	6.50- 8.50	10.00-12.00
40.	Waldorf Astoria (Headquarters Hotel, no rooms available)		
6.	Westbury, Madison Ave. at 69th St.	....	16.00
66.	Woodstock, 127 West 43rd St......	....	8.00-12.50
54.	Grand Central Palace..............	Location of exhibits	

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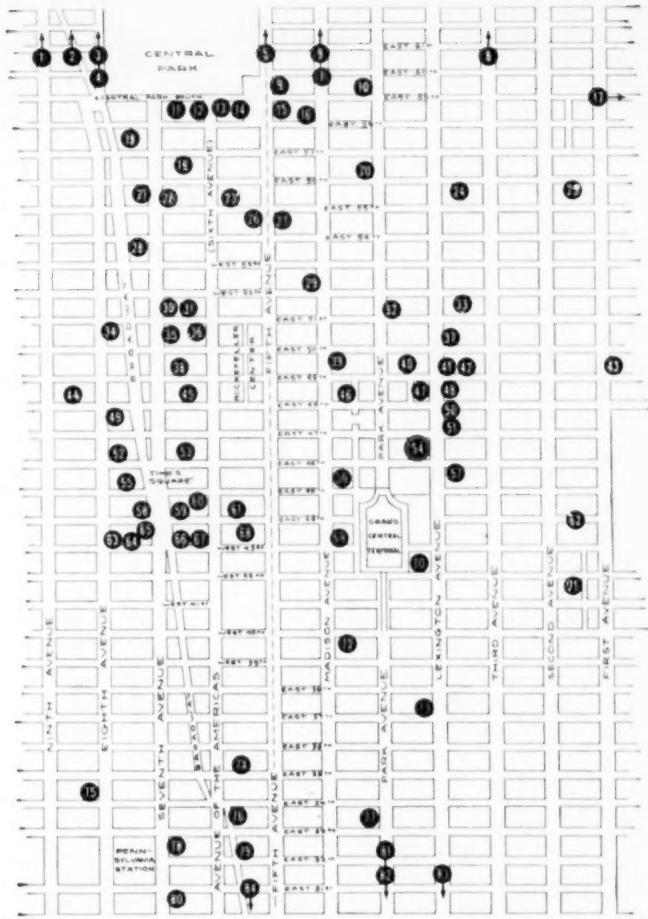
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